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**A REPORT BY THE DIVISION OF CARDIOLOGY
ST. MICHAEL'S HOSPITAL, UNIVERSITY OF TORONTO, ONTARIO**

Scientific Update™

The Importance of Prompt Blood Pressure Control to Target in High Risk Hypertensive Patients: The Valsartan Antihypertensive Long-term Use Evaluation (VALUE) trial

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Several classes of antihypertensive agents have been shown to reduce cardiovascular morbidity and mortality in the high-risk hypertensive population, however, large hypertension trials have yet to demonstrate significant differences between treatments. The question that remains to be answered is – do the different mechanisms of action of the antihypertensive drugs possess different cardiovascular protective properties beyond blood pressure lowering? The Valsartan Antihypertensive Long-term Use Evaluation (VALUE) trial was designed to test the hypothesis that for the same degree of blood pressure (BP) lowering, the angiotensin receptor blocker (ARB), valsartan, would reduce cardiac morbidity and mortality more than the calcium channel blocker, amlodipine, in high-risk hypertensive patients. The majority of enrolled patients were previously on antihypertensive therapy and were directly rolled over to randomized therapy consisting of a gradual up-titration of valsartan or amlodipine, with the addition of diuretics to achieve target BP. The late-breaking results of VALUE, as well as the clinical implications of the results, are the subject of this *Cardiology Scientific Update*.

The widespread use of antihypertensive drugs has led to a global reduction in the cardiovascular (CV) morbidity and mortality associated with hypertension.[1] The drug regimens shown to reduce CV events, either in placebo-controlled trials or in comparison with other effective antihypertensive drugs, include diuretics, ß-blockers, calcium channel blockers (CCBs), angiotensin-converting enzyme (ACE) inhibitors and, more recently, ARBs.[2-4] The availability of multiple antihypertensive drug regimens has led to some confusion for the practicing clinician, as well as uncertainty and ongoing debate among investigators, as to the comparability of the different regimens with respect to improving CV outcomes.[5] Over the past decade, several large hypertension trials with >100,000 patients involved the primary comparisons of CCBs or ACE inhibitors (the "new") with diuretics and/or ß-blockers (the "old"); these trials have not revealed significant differences in primary outcomes among the different study regimens.[6-10] On the other hand, in trials that were not designed primarily for hypertension, but involved a comparison of ACE inhibitors with placebo in patients with coronary artery disease (CAD), those at risk for CV events, as well as patients with a history of stroke, uniformly reported the benefit of ACE inhibition on CV outcomes.[11-13]

The ARBs constitute the newest class of agents approved for the treatment of hypertension. These agents are not only efficacious in lowering BP but, unlike other drug classes, are also remarkably well-tolerated.[14,15] To date, there are 3 large outcome trials of ARBs in hypertension.[3,16,17] The newest of the 3 trials – the VALUE trial – is the first ever to compare the ARB, valsartan, to a third-generation CCB, amlodipine. A CCB was used to determine if blocking the renin-angiotensin system (RAS) had a differential effect besides lowering BP by another pathway. The driving hypothesis for VALUE is that for the *same* degree of BP lowering, a valsartan-based BP-lowering regimen would be more effective than an amlodipine-based regimen in decreasing

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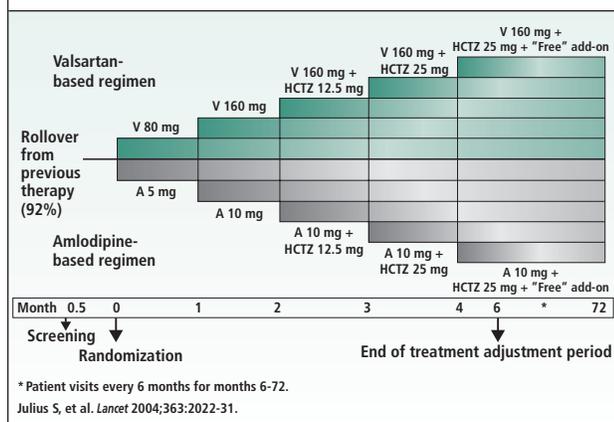Michael R. Freeman, MD

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Figure 1: VALUE study design[26]
Elective titration to target BP (<140/90 mm Hg)

*Patient visits every 6 months for months 6-72.
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V = valsartan, A = amlodipine, HCTZ = hydrochlorothiazide

cardiac outcomes, including acute myocardial infarction (MI), congestive heart failure (CHF), and cardiac mortality.[17] In patients with mild-to-moderate hypertension, valsartan has been shown to be equally effective in lowering BP, but is better tolerated than amlodipine.[18]

The rationale for choosing a dihydropyridine CCB like amlodipine as the active control was based on several criteria. First, amlodipine is one of the most widely prescribed anti-hypertensives in the western world.[19] Second, a long-acting dihydropyridine CCB was shown to reduce CV and total mortality when compared to placebo in the Syst-Eur trial,[20] in which the magnitude of mortality improvement was virtually identical to that demonstrated with "gold standard" diuretics and ß-blockers.[21] Despite earlier challenges from meta-analyses that related predominantly to the safety of the short-acting CCBs,[22] prospective studies have thus far demonstrated that CCBs are as clinically effective as diuretics and ß-blockers in the treatment of hypertension.[7,10] In addition, experimental and preliminary clinical data suggest that amlodipine may actually be antiatherosclerotic.[21,23-25] Accordingly, amlodipine likely has neutral cardiac effects and is, therefore, a fair and appropriate active control for the purpose of detecting any possible additional cardioprotective benefits associated with an ARB beyond BP control.

Study design and protocol

The rationale and the study design of VALUE have been published in detail.[17] The study included patients aged ≥50 years, with treated or untreated hypertension, and pre-defined CV risk factors that included:

- Diabetes
- Current smoking
- High total cholesterol
- Left ventricular hypertrophy by electrocardiogram
- Proteinuria

Table 1: Primary and secondary endpoints of the VALUE trial[26]

The primary endpoint was time to first cardiac event, defined as a composite of:

- Sudden cardiac death
- Fatal MI
- Death during or after coronary revascularizations
- Death associated with recent MI on autopsy
- Heart failure hospital admission
- Non-fatal MI
- Emergency procedure to prevent MI

Pre-specified secondary endpoints were:

- Fatal and non-fatal MI
- Fatal and non-fatal heart failure
- Fatal and non-fatal stroke

- Raised serum creatinine between 150 and 265 µmol/L.

CV disease factors:

- CAD
- peripheral artery disease
- cerebrovascular disease
- left ventricular hypertrophy with strain pattern.

Patients who were already on antihypertensive treatments first discontinued previous drugs and were immediately rolled over to 1 of 2 study arms (Figure 1). The protocol was designed with the anticipation that, by 6 months after randomization, both treatment arms would have achieved target BP control. The primary endpoint and pre-specified secondary endpoints of the VALUE trials are shown in Table 1. Two other pre-specified analyses were all-cause mortality and new-onset diabetes. The study was event-driven, 1450 patients with a primary event were required to provide 90% power to detect a 15% reduction (12.5% to 10.6%) in the primary endpoint with 14,400 patients.

Results

The primary results of VALUE have recently been presented and published.[26] Between September 1997 and November 1999, 15,314 eligible patients in 31 countries were randomized. Since 68 patients were excluded because of deficiencies in good clinical practice, there were therefore, 15,245 randomized patients included in the analysis. The mean follow-up was 4.2 years. The baseline characteristics, which have been published separately,[27] together with the qualifying risk and disease factors, are summarized in Table 2. The two treatment arms were comparable in all variables at baseline. Over one-third of patients had elevated cholesterol, diabetes, and existing CAD, attesting to their high risk. Of note, over 92% of the patients had been previously treated for hypertension – this included the use of ACE inhibitors (41%), CCBs (41%), ß-blockers (33%), and diuretics (27%). Among these patients, 37% were on monotherapy, 31% were on 2 agents, and 16% were on 3 agents.

Table 2: Baseline characteristics

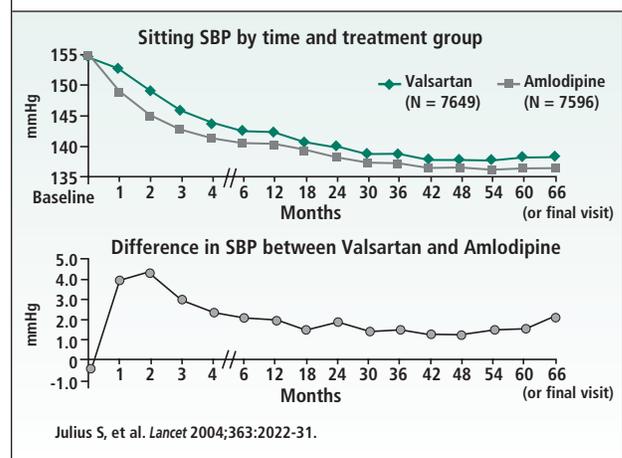| Demographics	Valsartan (n = 7649)	Amlodipine (n = 7596)
Women (%)	3240 (42.4%)	3228 (42.5%)
Age (y)	67.2 ± 8.2*	67.3 ± 8.1
BMI (kg/m^2)	28.6 ± 5.1	28.7 ± 5.0
Hypertension treated (%)	7088 (92.7%)	6989 (92.0%)
SBP (mmHg)	154.5 ± 19.0	154.8 ± 19.0
DBP (mmHg)	87.4 ± 10.9	87.6 ± 10.7
Heart rate (beats/min)	72.3 ± 10.8	72.5 ± 10.7
Race (%)	28.6 ± 5.1	28.7 ± 5.0
Caucasian	6821 (89.2%)	6796 (89.5%)
Black	325 (4.3%)	314 (4.1%)
Oriental	272 (3.6%)	261 (3.4%)
Other	231 (3.0%)	225 (3.0%)
Qualifying risk factors		
Elevated cholesterol	2395 (31.3%)	2428 (31.2%)
Diabetes mellitus	2555 (33.4%)	2522 (33.2%)
Current smoking	1826 (23.9%)	1838 (24.2%)
Proteinuria	1721 (22.5%)	1714 (22.6%)
LVH without strain pattern	954 (12.5%)	902 (11.9%)
Elevated serum creatinine	290 (3.8%)	260 (3.4%)
Qualifying disease factors		
Coronary heart disease	3490 (45.6%)	3491 (46.0%)
Peripheral artery disease	1052 (13.8%)	1062 (14.0%)
Stroke or TIA	1513 (19.8%)	1501 (19.8%)
LVH with strain pattern	454 (5.9%)	462 (6.1%)

BMI = body mass index; LVH = left ventricular hypertrophy;
SBP and DBP = systolic and diastolic blood pressure, respectively
TIA = transient ischemic attack

Although BP was reduced in both the valsartan- and amlodipine-based groups, the trial did not achieve the same level of BP control in the 2 groups (Figure 2). BP was lowered more in the amlodipine arm than in the valsartan arm: differences were 4.0/2.1 mm Hg (systolic/diastolic BP) in the early period, 2.1/1.6 mm Hg at 6 months, and stable at 1.5/1.3 mm Hg at 1 year. More patients in the valsartan-based groups received diuretics and other combinations or add-ons post-randomization. Furthermore, fewer patients in the valsartan group than in the amlodipine-based group reached the target systolic BP of <140 mm Hg (57% versus 63%).

Results of the primary composite endpoint (combined cardiac morbidity and mortality), the secondary endpoints (including the components of the primary cardiac endpoints and stroke), and the pre-specified analyses are summarized in Table 3.

There was no difference in the primary composite endpoint between the 2 study groups; cardiac mortality accounted for 30% (of which, sudden death accounted for 65%, fatal MI for 20%, and CHF death for 10%), whereas cardiac morbidity accounted for about 70%. For the secondary endpoints, total MI was significantly higher in the valsartan group; this was accounted for primarily by non-fatal MI (but not fatal MI).

Figure 2: Systolic blood pressure[26]

Sitting SBP by time and treatment group

Difference in SBP between Valsartan and Amlodipine

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When viewed over the entire study period, there was a trend towards a higher incidence of stroke in the valsartan group (p=0.08); however, for CHF, the trend favoured valsartan (p=0.12). All-cause mortality was not different between the groups. Of particular interest, there was a significant 23% decrease (p<0.0001) in new-onset diabetes with valsartan when compared to amlodipine in the 10,000 patients without diabetes at baseline.

Because of the differences in BP between the 2 groups, which was most pronounced earlier in the study (ie, in the first 6 months), the odds ratios of all of the pre-specified endpoints were calculated at sequential time intervals during the study (Figure 3). Odds ratios in favour of amlodipine were noted for most endpoints during the first 6 months, when the BP difference was the greatest. Thereafter, the odds ratios moved towards unity, except for CHF hospitalizations where there was a clear trend in favour of valsartan during the last 4 years. These time-dependent analyses therefore suggest that the trend for the more superior effect of amlodipine on most outcomes in the early
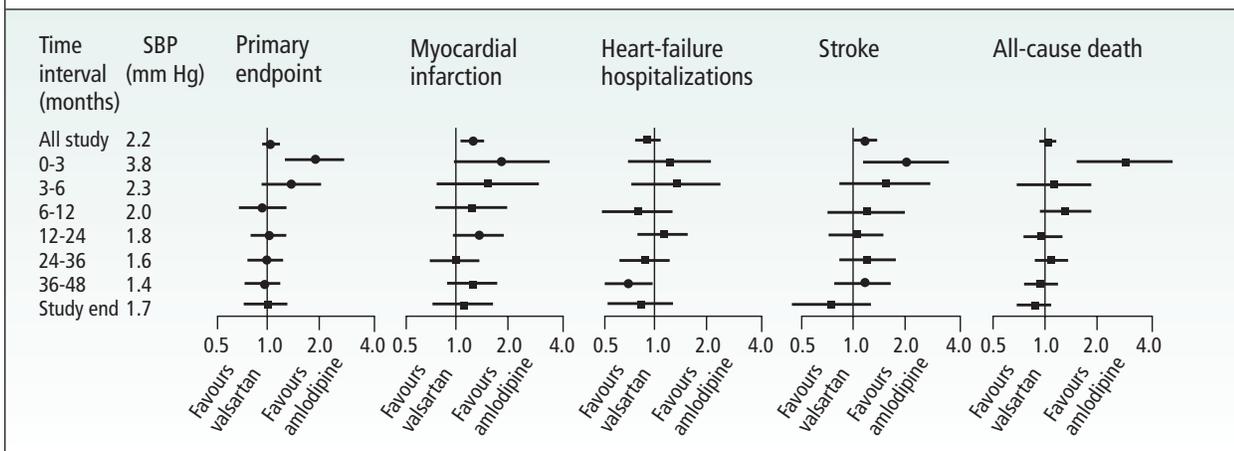
Table 3: All pre-specified endpoints and analyses

	Valsartan (n = 7649)	Amlodipine (n = 7596)	Hazard ratio (95% CI)	P value
Primary composite	810 (10.6%)	789 (10.4%)	1.04 (0.94-1.15)	0.49
Cardiac mortality	304 (4.0%)	304 (4.0%)	1.01 (0.86-1.18)	0.90
Cardiac morbidity	586 (7.7%)	578 (7.6%)	1.02 (0.91-1.15)	0.71
MI*	369 (4.8%)	313 (4.1%)	1.19 (1.02-1.38)	0.02
Heart failure*	354 (4.6%)	400 (5.3%)	0.89 (0.77-1.03)	0.12
Stroke*	322 (4.2%)	281 (3.7%)	1.15 (0.98-1.35)	0.08
All-cause mortality	841 (11.0%)	818 (10.8%)	1.04 (0.94-1.14)	0.45
New-onset diabetes**	690 (13.1%)	845 (16.4%)	0.77 (0.69-0.86)	<0.0001

* Fatal and non-fatal events;
** incidence rates were based on patients without diabetes at baseline

Figure 3: Differences in BP between groups with odds ratios for consecutive time intervals

Time interval (months)	SBP (mm Hg)	Primary endpoint	Myocardial infarction	Heart-failure hospitalizations	Stroke	All-cause death
All study	2.2					
0-3	3.8					
3-6	2.3					
6-12	2.0					
12-24	1.8					
24-36	1.6					
36-48	1.4					
Study end	1.7					

period may be accounted for by better control of BP that was no longer apparent after 6 months when these BP differences were attenuated.

To further assess the impact of adequate BP control on clinical outcomes, the odds ratios were calculated from patients who had their BP controlled (systolic BP <140 mm Hg) at 6 months versus those who did not have their BP controlled in both the valsartan and amlodipine groups.[28] As shown in Figure 3, the benefits of BP control at 6 months were very similar in patients receiving both regimens. Therefore, early BP control was a powerful determinant of almost all endpoints (except for MI) in both treatment groups.

A similar analysis to assess the BP dependency of the various outcomes was also conducted by comparing patients who responded at 1 month. Responders were defined as those patients who were previously treated and had no increase in systolic BP when switched to study drug, or those patients not previously treated in whom there was a decrease of ≥10 mm Hg. The point estimates were essentially the same as in the previous analysis of patients with controlled BP versus uncontrolled BP at 6 months.

The final additional analysis performed to address the issue of inequalities in BP was the use of a novel technique the investigators called "serial median matching."[28] The computer was programmed to select the most median patient (based on systolic BP) within the valsartan group and then paired with a patient from the amlodipine group matched for BP (within 2 mm Hg), age, sex, and previous coronary disease, stroke, and diabetes. This process was repeated until all eligible patients were included; thus 5006 comprehensively matched valsartan-amlodipine cohort pairs (n=10,012), with a mean systolic BP of 140 mm Hg in each drug group, were created. The hazard ratios for subsequent clinical events are shown in Figure 4. Most outcomes,
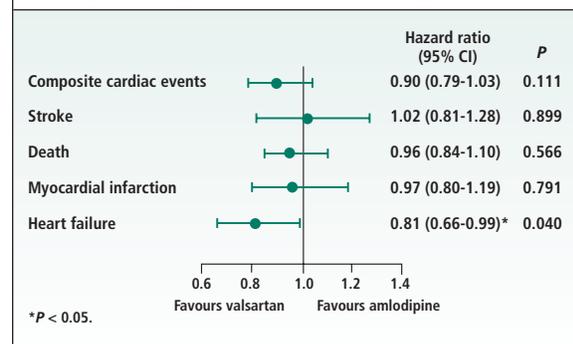
including the primary endpoint, were closely similar for the 2 arms, but notably, fewer hospitalizations for CHF occurred with valsartan. This again attests to the notion that valsartan protects from CHF beyond BP lowering.

Both the valsartan- and amlodipine-based regimens were well-tolerated with few severe adverse events. However, the most frequent adverse event, edema, was more than twice as common in the amlodipine group (32.9% vs 14.9%, $p<0.001$). Dizziness, headache, and fatigue were more common in the valsartan group, although the frequency of these events was low. A total of 911 patients (11.9%) in the valsartan group discontinued therapy because of adverse events, compared to 983 patients (12.9%) in the amlodipine group.

Discussion and implications

The results of the VALUE trial demonstrate that good BP control can be achieved with both valsartan- and amlodipine-based regimens, but the effect is more pronounced with

Figure 4: Major study endpoints in 5006 patient pairs (N = 10,012) on valsartan- or amlodipine-based therapies using serial median matching[28]

	Hazard ratio (95% CI)	P
Composite cardiac events	0.90 (0.79-1.03)	0.111
Stroke	1.02 (0.81-1.28)	0.899
Death	0.96 (0.84-1.10)	0.566
Myocardial infarction	0.97 (0.80-1.19)	0.791
Heart failure	0.81 (0.66-0.99)*	0.040

*$P < 0.05$.

amlodipine. Despite the unanticipated BP difference, the primary cardiac endpoint was not different between study groups. For the pre-specified secondary outcomes, stroke was lower – but not significantly – whereas MI was significantly lower in the amlodipine group. On the other hand, there was a persistent trend for less CHF in the valsartan group. The inequalities in BP in VALUE in favour of amlodipine throughout the trial preclude a proper comparison of CV outcomes and obligated several *post-hoc* attempts to overcome the impact of this unexpected result. These analyses, which are not part of the primary analyses, should therefore be interpreted with some caution. Nevertheless, the time-dependent analyses of odds ratios strongly suggest a BP dependency of most outcomes.

The observed differences in stroke rates may be best explained by between-group BP differences that were greatest in the first year. Indeed, 63% of the observed excess incidence of strokes occurred in the first 6 months of the study and 76% occurred within the first 12 months. In the case of CHF, early benefits of valsartan were probably masked by the lower BP achieved with amlodipine during the first 6 months. Point estimates that favoured valsartan-based therapy in the last 4 years suggest a positive impact of angiotensin blockade on CHF beyond that of BP lowering, a concept that is compatible with conventional wisdom.

The reason for the more superior effect of the amlodipine-based regimen in VALUE is unclear. The usual clinical dose range for valsartan is 80-160 mg daily. It was subsequently found that higher doses were required for full angiotensin II blockade[29] and, indeed, the US Drug and Food Administration has recently approved a dose range of 160-320 mg for the treatment of hypertension (not applicable to Canada). It is conceivable that if a valsartan dose regimen of 320 mg per day was used – the same high dose has also been demonstrated to improve clinical outcomes in chronic CHF and post MI[30,31] – the BP response would have been comparable to, or better than, amlodipine, and a benefit of valsartan on cardiac outcomes may have been discerned.

The 23% reduction in new-onset diabetes with valsartan is particularly interesting, given that the comparator, amlodipine, is a CCB, which is generally considered to be metabolically neutral. In terms of an absolute risk reduction, treating about 30 patients over 4 years will avert 1 new case of diabetes. The Losartan Intervention For Endpoint reduction in hypertension (LIFE) and Study on Cognition and Prognosis in the Elderly (SCOPE) trials also demonstrated a lower incidence of new-onset diabetes in the ARB group,[16,32] although in the LIFE study[32] it cannot be ascertained whether the benefit was really due to blockade of angiotensin or an adverse effect of ß-blockade on glucose balance.[33] In the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT), although

a direct comparison was not made, the lisinopril-treated group also had a lower incidence of new-onset diabetes when compared to the amlodipine-treated group.[6] In the HOPE study, ramipril reduced new-onset diabetes compared with placebo.[34] Together with the results of VALUE, one can therefore conclude that blockade of the renin-angiotensin system exerts preventive effects on diabetes development. These findings are relevant because diabetes greatly increases the CV consequences of hypertension; patients with even uncomplicated hypertension frequently have insulin resistance[35] and patients with new-onset diabetes have demonstrated an equally poor prognosis as patients with known diabetes.[36] The beneficial consequence of reducing the risk of new-onset diabetes (ie, the use of ACE inhibitors or ARBs), or the adverse consequence of increasing new-onset diabetes (ie, with the use of diuretics),[6] may take many years to become apparent, a time period that is likely beyond the follow-up duration of most published hypertension trials.

What are the clinical implications of the VALUE trial? For scientists and clinical investigators, the results of VALUE will undoubtedly influence the future design, conduct, and analysis of hypertension trials, with the appreciation that in high-risk patients, even minute differences in BP within the high-to-normal range will influence cardiac outcomes, a concept that is supported by a recent meta-analysis.[37] Additionally, the results of VALUE may prompt investigators to re-evaluate the results of published clinical trials, particularly the comparison trials where conclusions were drawn without a critical review of the differences in BP and the importance of new-onset diabetes.[6] One should also realize that the majority of patients in VALUE were rolled over from active therapy, a situation that is not frequently encountered in practice. On the other hand, a systolic BP of 155 mm Hg, the baseline value in VALUE, is frequently the BP that physicians treat. For clinicians who manage patients with *high-risk* hypertension, the treatment goal will be to reach the recommended target BP in a relatively short duration, ie, in weeks rather than in months as adopted in many previous clinical trials. In terms of the impact of VALUE on current treatment guidelines[2,4,38] – recommending the use of combination therapy for optimal BP control – a possible approach may be to initiate treatment with combination therapy in patients who are deemed high risk for CV events.

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