Influence of the Angiotensin II Antagonist Valsartan on Left Ventricular Hypertrophy in Patients With Essential Hypertension

To the Editor:

The recent article by Thürmann et al.1 is of substantial interest in documenting efficacy of a relatively new angiotensin II antagonist for reduction of left ventricular mass in hypertensive patients. However, some features of the study cast doubts on the validity of the results. Moreover, misstatements of fact concerning existing literature further impair the interpretation of these data.

Although the authors report the efficacy of valsartan for regression of left ventricular hypertrophy (LVH), in fact, only the mean reduction of left ventricular (LV) mass is reported rather than the number of individuals with LVH who had sufficient reductions of LV mass to revert to normal. More importantly, despite the emphasis on the efficacy of valsartan, the investigators’ data indicate that LV mass was reduced with atenolol as well. It is unclear whether the reduction of LV mass with atenolol was significantly less than that with valsartan. It can be questioned whether the ~10 g average difference in LV mass reduction between valsartan- and atenolol-treated patients is biologically or even statistically meaningful. Additionally, there appeared to be equivalent reduction of LV wall thickness with atenolol and with valsartan.

More importantly, the study was not a comparison of single-drug therapy. A third of the patients in both groups received hydrochlorothiazide to achieve hypertension control. Other patients received pretreatment with diuretics, which was considered acceptable because the investigators believed that the effects of diuretics on LV mass and wall thickness have been shown to be negligible. In fact, single-drug comparative studies, including some of those quoted by the authors, have shown substantial efficacy of diuretics for reduction of LV mass, wall thickness, and cavity size.2-5 It would have been useful to analyze the data with adjustment for the use of hydrochlorothiazide or to have performed a subgroup analysis of patients who did not receive a diuretic. In the present study, hydrochlorothiazide may have accounted for LV mass reduction by its individual action or by acting synergistically with either or both of the 2 study drugs.

Comparative trials of antihypertensive therapy for reduction of LV mass need to include single-drug comparisons of sufficient duration. Assumptions of lack of efficacy of diuretic therapy for LV mass and wall thickness are not supported by the results of recent trials. When patients require medications to control blood pressure other than those described in the hypothesis of the study, intention-to-treat analyses of LV mass reduction are likely to show the effects of the intention rather than the treatment. Neither efficacy of valsartan nor its superiority to atenolol for reduction of LV mass is proven by the present study.

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Response

In reply to the comments of Dr Gottdiener, we want to emphasize that the main objective of our trial was the evaluation of the effect of the angiotensin (AT₁)-receptor antagonist valsartan on left ventricular hypertrophy (LVH).1 A control group was chosen for reasons of trial design and blinding.2

A reduction of left ventricular mass index (LVMI) of $\pm 10\%$ or normalization ($<134 \text{ g/m}^2$ in men and $<110 \text{ g/m}^2$ in women) occurred in 72% of patients in the valsartan group and in 68.2% in the atenolol group, indicating no difference in this regard. The 90% CI for the reduction of LVMI comparing valsartan with atenolol was stated as 0.85 to 0.97; $R = 0.91$. This was not statistically significant. Posterior and end-diastolic wall thicknesses were reduced by 1.2 and 1.5 mm (each $P<0.0001$), respectively, after valsartan and by 0.8 and 1.0 mm, respectively, after atenolol ($P<0.005$ and $P<0.0001$), showing a marginal difference between treatments.

Nineteen percent of patients in the intent-to-treat population had prior exposure to antihypertensive therapy (for $<4$ weeks), and 1 patient in each treatment group had received a diuretic during the 12 months before the trial.

Antihypertensive monotherapy may not be sufficient in most patients with end-organ damage. Therefore, about one third of our study population required additional medication to ensure adequate blood pressure control. Addition of hydrochlorothiazide (HCTZ) was required to the same degree in both groups and was therefore of comparable benefit in both treatment groups. It remains unproven whether combination treatment with an AT₁-receptor antagonist and a diuretic exerts a significantly higher pharmacological synergy than the combination of atenolol and HCTZ. Therefore, a statistical analysis excluding patients with diuretic cotreatment was not performed.
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Overlap Analysis of the West of Scotland Coronary Prevention Study (WOSCOPS)

To the Editor:

The results of the above article are being used for pharmaceutical promotion for prescribing pravastatin.1 The overlap analysis in this article is interpreted as suggesting that pravastatin reduces mortality over and above its effect on serum cholesterol. We believe that this assertion may not be justified.

The case comparison might not be valid in this analysis. The sample selection was based on on-treatment rather than baseline LDL cholesterol for both placebo and pravastatin groups. The baseline LDL cholesterol levels were clearly different between the 2 groups. The pravastatin group started with higher LDL cholesterol levels, and therefore those in this group were of a greater cardiovascular risk and had more room for risk reduction with active treatment. In contrast, the placebo group had low baseline LDL cholesterol levels, suggesting inherently lower baseline cardiovascular risk. It is not difficult to appreciate that the magnitude of any given favorable effect is far greater when interventions are directed at high-risk groups. The overlap analysis compared 2 groups with very different baseline risks.

To conclude that pravastatin has additional effect over and above its effect in lowering cholesterol, the analysis would need to be controlled for the change in lipids rather than for the on-treatment lipids values. Because the study failed to find a direct correlation between the reduction in LDL cholesterol and mortality, this confounder perhaps cannot be accounted for statistically.

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Response

We thank Drs Lim and Yee for their comments on our overlap analyses. In this comparison of the 2 treatment arms of the study, we asked the question whether subjects who lowered their LDL cholesterol with pravastatin achieved the risk usually associated with that lower level. We agree that those treated with the drug would initially have been at a high baseline risk due to their high LDL cholesterol level. It was anticipated that over 5 years, the risk in the pravastatin-treated subjects would approach that seen in individuals who habitually had the lower LDL level. The fact that treatment reduced the risk to a value significantly lower than that of matched controls is both remarkable and unexpected.

The analysis proposed by the correspondents, examining the change in LDL, would be confounded fundamentally by the drug-treatment effect and is therefore inappropriate.

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Prospective Study of a Self-Report Type A Scale and Risk of Coronary Heart Disease: Test of the MMPI-2 Type A Scale

To the Editor:

Kawachi et al1 report that type A behavior, as measured by the Minnesota Multiphasic Personality Inventory (revised) (MMPI-2), is an independent predictor of coronary heart disease death, nonfatal myocardial infarction, and angina, even after controlling for anger and cynicism, also measured by the MMPI-2. This is the first study to validate the predictive validity of the MMPI-2 for cardiac end points. The risk ratios observed were moderately strong, although not as strong as those previously observed for other measures of emotional distress (eg, the Beck Depression Inventory and the Crown-Crisp Phobic Anxiety Inventory). Because measures of different types of emotional distress are always confounded, the independence of the type A behavior scale above and beyond these other scales remains unclear. More importantly, the claim that this scale is independent of anger is dubious given that a dose-response relationship exists between severity of coronary artery disease and denial of anger2,3 as measured by discrepancies between frequency ratings from patients and a person they select as “someone who knows you well.” For males at least, the more severe a person’s coronary artery disease, the more likely the patient is to deny anger relative to a significant other’s rating of anger frequency.3 Approximately 40% of males from a catheterization laboratory sample
display denial of anger, and denial predicts a 4.4-fold increased relative risk for death over 5 years.5

Thus, any study that uses only self-reported anger provides little in the way of valid understanding. Apart from randomly assigned, controlled intervention trials, perhaps the most pressing need in clinical care of stress in the ischemic heart disease patient is a test of the relative power and independence of these various scales. Once a scale (or scales) emerges as the strongest and most independent predictor(s) of outcomes, it will be possible to make authoritative recommendations for clinical screening.

Mark W. Ketterer, PhD
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Response

We thank Dr Ketterer for drawing our attention to the finding that a dose-response relationship exists between severity of coronary artery disease and denial of anger. We would point out, however, that in both our recent study linking type A behavior to risk of coronary disease1 and our earlier report of an association between coronary artery disease and denial of anger, we strongly agree with Dr Ketterer that better studies are needed to establish the differential predictive power and independence of various states of emotional distress (eg, depression, anxiety, and anger) in relation to coronary disease risk.3

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Estimation of Oxygen Delivery in Newborns With a Univentricular Circulation

To the Editor:

The article by Barnea et al1 entitled “Estimation of Oxygen Delivery in Newborns With a Univentricular Circulation” provides an interesting mathematical analysis of tissue oxygen delivery.

However, their interpretation of Equation 5 (Equation 1 below) is misleading.

\[
1. \quad DO_2 = CAO_2 \cdot QS = \frac{1}{1 + Qp/Qs} \cdot CO \cdot CPV_{O_2} - \frac{1}{Qp/Qs} \cdot CV_{O_2}
\]

They conclude that systemic oxygen delivery (DO2) is a complex function of cardiac output (CO). This is not strictly true, because replacement of Qs+Qp (systemic plus pulmonary blood flow) by CO (their Equation 3, Equation 2 below) in the first part of Equation 1 yields Equation 3 below, because the term CO cancels itself out.

\[
2. \quad CO = Qs + Qp
\]

\[
3. \quad DO_2 = CAO_2 \cdot QS = Qs \cdot CPV_{O_2} - (Qs/Qp) \cdot CV_{O_2}
\]

Thus, DO2 is dependent on the systemic blood flow and on the reciprocal of the shunt ratio Qp/Qs and not on CO, as they deduce.

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Response

We thank Dr Poullis for his interest and are glad that our articles are stimulating new ideas.1,2 In our initial mathematical analysis, we developed an equation (Equation 1 in Dr Poullis’ letter) that related systemic oxygen delivery to cardiac output, the ratio of pulmonary to systemic blood flow (Qs/Qp), the oxygen content in pulmonary venous blood, and whole body oxygen consumption. Each of these variables can be independently changed. For example, cardiac output can be changed without the necessity of altering Qs/Qp.

By making a substitution of variables, Dr Poullis develops another equation (Equation 3 in his letter). This equation presents systemic oxygen delivery as a function of systemic blood flow (Qs), Qs/Qp, the oxygen content in pulmonary venous blood, and whole body oxygen consumption. Although the equation is mathematically valid, the conclusion that systemic oxygen delivery is not a function of cardiac output is invalid. Dr Poullis includes Qs/Qp ratio and Qs as 2 independent variables. This, of course, is not the case. In Dr Poullis’ equation, Qs/Qp cannot be changed without altering Qs, and Qs cannot be changed without altering Qp/Qs. Dr Poullis’ equation also begs the question, how does Qs change? Without changing Qs/Qp, Qs can only change to the Editor:


Response

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by changing cardiac output. Therefore, in his equation, systemic oxygen delivery is a function of cardiac output as well, only here cardiac output is implicit and hidden behind $Q_S$.

Although there are many ways to express these equations, the goal should be kept in mind: the perioperative management of children with hypoplastic left heart syndrome. Given the small patient size and precarious hemodynamics, it is difficult to make measurements. For this reason, we developed a simple model to evaluate the ability of blood gases–derived indexes to monitor systemic oxygen delivery.1,2 This mathematical analysis awaits clinical studies to find the best way to monitor these patients and save lives.3,4

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Estimation of Oxygen Delivery in Newborns With a Univentricular Circulation
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