The Valsartan Antihypertensive Long-Term Use Evaluation Trial
A Study in Contrasts

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The Valsartan Antihypertensive Long-Term Use Evaluation (VALUE) trial was designed to test the theory in hypertensive patients determined to be at high cardiovascular risk that, for the same level of blood pressure (BP) control, valsartan would reduce cardiac morbidity and mortality more so than amlodipine. The noise level about this trial was high in the months leading up to the release of its findings in 2004. Shortly after its publication, however, the preceding din became barely audible, particularly with regard to the usual deluge of poststudy publications and, thus, the sway of positive study results (or not) to drive publication numbers for an outcomes study. As an example of this, the Losartan Intervention for End-Points (LIFE) study was positive on several accounts, and, on a careful review of PubMed citations, it was found to have generated 105 original publications in indexed journals through June 2006, whereas, to date, there have been a mere handful of original publications from the VALUE trial.

The VALUE trial fell short of being able to test its proposed hypothesis, because the prerequisite of equal BP pressure reduction between therapies was not realized. Not surprisingly, a significant BP difference in favor of amlodipine existed, particularly in the early months of the trial. This failure to achieve equivalent levels of BP reduction, in part, was because of the mistaken belief that angiotensin-receptor blocker (ARB) monotherapy, and in this case valsartan, would reduce BP equally as well as amlodipine in a preponderance of high-risk subjects. In the current era of ARB use, such an assumption would not have been made, whereas a decade ago, when the VALUE trial was designed, we had but an embryonic understanding of how well and in whom ARB monotherapy best worked, thus the flawed trial design by our current understanding of this drug class.

Despite the main VALUE trial being unable to prove its primary hypothesis, important bits of information did emerge. First, it showed that BP reduction per se, rather than angiotensin II antagonism, is the key to cardiovascular prevention and that immediate BP lowering and early (within 6 months) BP control are critical determinants of cardiovascular outcome. On both accounts, amlodipine proved superior. Alternatively, in the VALUE study, both the rate of new-onset diabetes and the incidence rate for heart failure were lower in valsartan-treated patients.

It is on this backdrop that these additional findings from the VALUE trial turn up. The VALUE trial had opted for a titration scheme of the double-blind study medication, which maximized the prospects of testing their primary hypothesis; thus, unlike the LIFE trial, where a diuretic was added before any upward titration of losartan, the VALUE study first titrated valsartan from 80 to 160 mg/daily or amlodipine 5 to 10 mg/daily before hydrochlorothiazide could be added as needed for further BP reduction. If the goal BP of <140/90 mm Hg was reached with either monotherapy, that dose was continued until the time to first cardiac event or study withdrawal.

Of the 15,245 patients in the VALUE trial, some 46.4% or 7080 (valsartan [n=3263] and amlodipine [n=3817]) remained on monotherapy at the end of the initial drug adjustment period with an average time on medication of 4.1 years. Juluis et al in this issue of the journal carefully and objectively describe the results of a straight comparison between valsartan and amlodipine albeit a post hoc and unplanned analysis. Most other megaclinical trials have been unable to undertake such a pure head-to-head drug comparison because of the need to frequently add other drugs to achieve the requisite level of BP control. Although this represents a subanalysis of the original VALUE data, the valsartan and amlodipine treatment groups were well-matched for demographic and concomitant disease factor variables; therefore, this aspect of such a post hoc subgroup analysis is minimally concerning.

BP reduction and control rates in the amlodipine and valsartan monotherapy treatment groups were comparable, and there was no early BP gradient as was seen in the main trial. This level of BP response would not have been unexpected considering that, compared with the remainder of the VALUE participants, the monotherapy patients had a lower baseline BP, a milder baseline cardiovascular risk profile, and, on average, had been more frequently treated with 1-drug therapy before randomization. All of these variables, together with the preponderance of whites in the study, would predict a strong likelihood of reaching goal BP with valsartan monotherapy and, thus, a better chance of matching the BP reduction seen with amlodipine monotherapy.

Not unexpectedly, there was a much lower in-trial event rate in these monotherapy groups. Of note, the myocardial infarction (MI) rates, which were lower with amlodipine in the main trial, were comparable between treatment groups in this substudy. This observation supports the argument that the reported MI difference in the main trial might have reflected...
BP differences in the early stages of the trial. The heart failure rate in this substudy also was less in the valsartan monotherapy group. This observation is now one of several that suggest that dihydropyridine calcium-channel blocker therapy, irrespective of the observed BP reduction, does not offer the same cardioprotection as is seen with compounds that interfere with renin–angiotensin system activity. Although this was a decidedly lower risk population, it still remains to be determined whether these valsartan-related findings are generalizable to primary prevention in hypertensive patients with truly uncomplicated disease.

What more might we learn from this particular data set? In the interpretation of clinical trial results with ARBs, the mean reduction in BP (which is typically significant) should be distinguished from the percentage of individuals who are poor, average, and excellent responders (which may vary considerably in different studies). We do not have such descriptive information from these studies nor do we have the numbers of patients whose BP was controlled at the low-end monotherapy dose level. The average daily valsartan and amlodipine use was 117 and 7.1 mg/day, respectively, which would suggest that a not-insignificant number of patients were controlled at the entry level dose for valsartan and amlodipine. If so, this is further evidence that this was a group of patients with an exceedingly mild form of hypertension and not the high-risk patient type originally proposed for study.

The limitations of this study are obvious and rest on how much credence can be attached to a subgroup analysis from a large randomized clinical trial. In an ideal world, this monotherapy comparison should have been a planned analysis, otherwise we are faced with a situation not dissimilar to placing a bet on a horse some time after having viewed the race. Why this analysis was unplanned related at least, in part, to the rather firm opinion held at the time of study inception that valsartan was equal to, if not more potent than, amlodipine. This was a strategic miscalculation. Yet, this subgroup analysis does offer us new insights; however, these data must be viewed in a circumspect manner considering that the subgroup characteristics of these monotherapy groups were overly homogeneous compared with the heterogeneous ethnic, age, and body size characteristics of the United States hypertensive population. These data should, however, strengthen the argument for a more careful comparative study of various pharmacotherapies for stage 1 hypertension.

Disclosures

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References

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