Are the Eutrophic Effects of Angiotensin Receptor Blockers Real?

To the Editor:

In a laborious experimental study, Savoia et al concluded that the addition of valsartan but not atenolol to the antihypertensive treatment decreased the resistance artery media/lumen ratio of diabetic patients. On the basis of such a finding, the authors suggest that it may be preferable to achieve tight blood pressure (BP) control by using angiotensin receptor blockers in addition to other antihypertensive agents to improve vascular structure and reduce cardiovascular risk in diabetic hypertensive patients. I do believe that this advantage was not clearly demonstrated in this study, and even if it was done, it could not be extended to other antihypertensive agents.

The lower efficacy of atenolol in terms of prevention of cardiovascular events was demonstrated repeatedly in elderly patients. At least in this age group, atenolol should not be used anymore as first-line therapy or as a comparison drug in clinical trials. Probably most of the lower efficacy of atenolol in this setting is attributable to a lower BP-lowering effect in this age group, a phenomenon evident in the first 6 months of the Anglo-Scandinavian Cardiac Outcomes Trial-Blood Pressure Lowering Arm trial. In the experiment of Savoia et al, patients were 60 years old, on the average, in the atenolol group. The authors assumed that BP did not vary between groups at the end of the experiment, but the data suggest the contrary. Systolic BP was 4.8 mm Hg lower in the valsartan group, and pulse pressure 2.4 mm Hg. The absence of formal statistical significance may be secondary to a $\beta$ error, in view of the small sample size of the experiment. Moreover, similar office BP values may conceal substantial differences in BP along the 24-hour period, as was shown in the Heart Outcomes Prevention Evaluation trial.

My main point, however, is related to the statistical analysis of this experiment. The analysis based on the within-group statistics in experiments with 2 groups is questionable. The right approach seems to be to perform a between-group comparison of changes of variation in the media/lumen ratio or any other parameter or to use the significance of F value for the group/time interaction in repeated measurements and the multiple factors ANOVA procedure. In addition, the groups differed substantially in terms of potential confounding variables, such as age (patients in the atenolol group were 4.5 years older, on average), baseline diabetes control (worst in the valsartan group), and mainly BP at the end of and presumably during the experiment. An ANCOVA procedure for changes (after minus before values) of the media/lumen ratio controlling for confounding is required in this case to identify an independent drug effect. And finally, media thickness was unchanged in both groups after the experiment, showing that the effect, if any, was restricted to arteriolar lumen (again a trend, not statistically significant), in accordance with the between-group difference in BP.

These shortcomings cast doubt on the internal validity of this experiment, which does not support the preference for any type of antihypertensive agent to reach tight BP control in patients with diabetes. The importance of the BP versus eutrophic effects of antagonists of the renin–angiotensin system is still an open issue and requires further clinical and experimental investigations.

Disclosures

None.

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