Commentary on Kostis' Report From SOLVD

We read with interest the paper by Kostis reporting the results of a retrospective analysis of a subset of hypertensive participants in the SOLVD trials. The conclusion that enalapril treatment was associated with diminished cardiovascular morbidity and mortality in this subset is consistent with the findings in the total population of SOLVD participants as well as with findings of several similar reports of studies in hypertension and cardiac disease, using a variety of other angiotensin converting enzyme (ACE) inhibitors. We are gratified that these results add one more piece of evidence in support of the thesis we have proclaimed for the past several years, ie, that in the absence of specific indication for other agents or contraindication against ACE inhibition, ACE inhibitors are probably the drug of first choice in treating hypertension.

Nevertheless, a few points from that paper need further clarification in order to better substantiate the conclusion:

1. Were there differences in the baseline characteristics between patients randomized to enalapril and placebo in the subset of hypertensive patients?
2. What was the overlap of the hypertensive subset, ie, how many participants had normal blood pressure also had elevated diastolic blood pressure?
3. What was the effect of enalapril on blood pressure in the hypertensive and nonhypertensive subsets?
4. What was the time course of the effects of enalapril in decreasing events?

We would be interested to see the author's comments on these points.

REFERENCES


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Questions Regarding Kostis' Article on SOLVD

First, please allow me to express my sincere gratitude to you and all your superb colleagues in maintaining the universally accepted integrity of the American Journal of Hypertension and improving on it in every issue. Thank you.

I read with great interest the article by our mutual friend and colleague, Dr. John B. Kostis.1 I believe the findings of this ancillary study to the Studies of Left Ventricular Dysfunction study (SOLVD), with regards to the treatment of hypertension, will be of great interest to the members of the JNC in formulating their JNC-VI report, which I am told is already being planned. I have a few questions regarding Dr. Kostis' article. These are as follows:

What were the original selection criteria for patients with hypertension who were randomized into SOLVD? Were they all on antihypertensive treatment? If yes, for how long and on what class of drugs? What was the average (and the range, if available) duration of hypertension? What was the distribution of these hypertensive patients, who by definition must have had an ejection fraction of ≤ 0.35, by the presence or absence of "overt heart failure"? What is meant by the statement that all those with "uncontrolled" hypertension were excluded? And, finally what was the actual blood pressure response in these two classes of hypertensive patients, and what was the difference between those on active drug and those on placebo?

What was the statistical power of SOLVD in detecting the difference in mortality and morbidity among those with history of hypertension and those without (eg, for CHF 16.7 v 20.6, as shown in Dr. Kostis' Table 1)? If 2,652 participants had a history of hypertension, then what is the meaning of the statement that the trial was not "sufficiently powered to detect differences within these small subgroups"? Given the demonstrated efficacy of enalapril in preventing CHF in patients with an ejection fraction...
I am pleased to respond to the questions raised by Dr. Irene Gavras and Dr. Harry Gavras on the paper "The Effect of Enalapril on Mortal and Morbid Events in Patients With Hypertension and Left Ventricular Dysfunction" (Am J Hypertens 1995;8:909-914). The scientific community is well aware both of their pioneering work in the clinical development of ACE inhibitors and of their continuing contributions in the field of hypertension. Below are the data they request.

Baseline characteristics in the placebo and enalapril groups in the two hypertension subsets are shown in Table 1. Among the 26 comparisons made, there was only one statistically significant difference between enalapril and placebo groups: in patients without myocardial infarction among patients with systolic blood pressure (SBP) $\geq 140$ mm Hg, diastolic blood pressure (DBP) $\geq 90$ mm Hg (1,508 and 985 participants, respectively) separated from the total number of those with a history of hypertension (N = 2,652). Were the outcome results similar in all three groups if there was no overlap between them, as stated on page 911? Were the final results, as presented, adjusted for differences between groups at baseline? If so, how was the adjustment made? Was there any interaction between any of the commonly recognized confounders and the effect of enalapril on blood pressure and the trial's endpoints? The statement that there were no "interactions" does not seem to be enough. These should be presented and discussed in detail.

All and all I enjoyed reading this article, and hope that the distinguished editors and the author would consider my questions worthy of a reply.

REFERENCES


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Responses From Dr. Kostis Regarding Questions on the SOLVD Data

SOLVD patients with elevation of SBP at baseline (761 randomized to placebo and 747 randomized to enalapril) and 985 patients with elevated DBP at baseline (481 randomized to placebo and 504 randomized to enalapril). Of these, 576 patients had elevation of both systolic and diastolic blood pressure (285 randomized to placebo and 291 randomized to enalapril). Analysis of this subset was not done because of its smaller size and the significant overlap (58%) with the subset of elevated diastolic blood pressure.

Enalapril use was associated with a lowering of the systolic and diastolic blood pressure in all patient subsets. The mean blood pressure at baseline and at year one and year two of follow-up in the different hypertensive and normotensive subsets is shown in Table 2. All differences between enalapril and placebo were statistically significant with $P < .01$ with two exceptions: at year one the difference in DBP in the subgroup with high SBP and high DBP was statistically significant with $P = .04$, and at year two differences in both DBP and SBP were not statistically significant in this smaller subgroup. Overall, the average difference in blood pressure between the placebo and enalapril groups was 6/4 mm Hg.

When the data were analyzed according to the change of blood pressure between baseline and the 6 weeks follow-up visit, a beneficial effect or trend of enalapril on morbidity and mortality was observed at