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Discussion VII

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U. Elkayam: Dr. Pitt, was the need to start angiotensin-converting enzyme inhibitors an end point in the SOLVD study?

B. Pitt: We looked at the need for additional heart failure therapy, including the need for diuretics and converting enzyme inhibitors. Both were required more frequently in the enalapril group than in the placebo group.

R. Cody: Dr. Benedict, I am impressed by two observations. First, with few exceptions, plasma norepinephrine levels in both the SOLVD and the SAVE trials were within the normal range. Second, despite the normal hormonal background, angiotensin-converting enzyme inhibitors produced a favorable effect that far exceeded what most investigators would have predicted in early heart failure. Given these observations, what is the role of measuring plasma neurohormonal levels in the future?

C. Benedict: Let me respond to your first question. The norepinephrine levels in the SOLVD prevention trial patients are closer to normal than the levels in the SOLVD treatment trial. However, the levels in both groups were significantly higher than values in control subjects.

S. Yusuf: It is true that the mean levels of neurohormones are significantly higher in the SOLVD trials. However, only a minority of patients in the SOLVD trials had a value that is >1 SD greater than the mean of the control group. It is possible that our definition of normal should be lowered or, alternatively, only a minority of patients exhibit activation of the neurohormonal system. It would be interesting to understand this heterogeneity.

C. Benedict: Although mean levels were relatively low, there are many patients who have very high neurohormonal values. Could such patients be selected and studied prospectively in future trials? By selecting such patients, we may be able to conduct trials with fewer patients.

B. Pitt: In response to Dr. Cody's comments, plasma renin levels in the SOLVD prevention trial were low, but those levels were measured at rest. Perhaps, renin levels in patients with heart failure would be more easily distinguished from placebo if they were measured during exercise.

M. Packer: Dr. Benedict, you analyzed the predictive value of baseline neurohormonal measurements in all of the patients in the study, but I am not sure that this is the correct approach. It is important to look at the predictive values of baseline measurements only in the patients who received placebo. To the extent that activation of the renin-angiotensin system plays an important role in the progression of heart failure, we might expect plasma renin activity to predict survival in such patients (as other studies have shown). However, since the influence of the renin-angiotensin system would be blocked in patients receiving a converting enzyme inhibitor, we would not expect plasma renin activity to predict survival in patients receiving enalapril. Support for my point comes from the CONSENSUS trial. In that study, values for plasma renin activity at the time of entry into the study predicted survival in the patients randomized to placebo, but not in those randomized to enalapril. A similar analysis should be carried out in the patients enrolled in the SOLVD trial. If you look at the predictive value of baseline measurements for all patients (combining those randomized to placebo and enalapril), you lose the ability to detect important correlations in specific subgroups.

J. Cohn: The point that Dr. Packer just made about renin is true. Renin is a univariate predictor of survival in the placebo arm and even in the treatment arm, but in our experience, it is not a predictor in a multivariate model, when you consider norepinephrine concomitantly.

M. Packer: The predictive value of neurohormonal measurements may depend on the patient population being evaluated. In patients with mild to moderate heart failure, plasma norepinephrine is a more powerful predictor of survival than is plasma renin activity. In contrast, in our experience and in that of Dr. Jean Rouleau from the University of Sherbrooke, plasma renin activity is the most powerful predictor of survival in patients with severe heart failure.

J. Cohn: If you study patients in functional class IV, I agree with you completely.

M. Packer: I think it is worth emphasizing that the systems used to classify the mode of death in patients with chronic heart failure are vague at best and arbitrary at worst. Nevertheless, it is important to make sure that all of the data in an individual trial are collected using uniform criteria. That is why it is essential that the classifications of mortality performed by each investigator be reviewed by a central

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committee that uses prospectively defined criteria. A central committee reviewed all of the mortality data in the V-HeFT and SAVE trials but not in the SOLVD trial. In the SAVE trial, the Mortality Classification Committee modified one-third of the mortality classification decisions made by the investigators.

J. Cohn: The Mortality Classification Committee changed about 25% of the decisions of the investigators in the V-HeFT study.

S. Yusuf: Who is right? The committee or the investigator?

J. Cohn: There are problems when a trial relies on the classification of the investigator without oversight by a central committee. Investigators do not use uniform criteria and are often influenced by extraneous physiologic data; for example, they will classify the death of a patient with a low ejection fraction as due to progressive heart failure even it is sudden. Knowing the ejection fraction influences the classification. I think we need to be very cautious about reaching conclusions about the mechanism of death when the classification system varies from study to study.

S. Yusuf: Whatever your concerns may be, I would emphasize that the results of three large, randomized trials that compare an angiotensin-converting enzyme inhibitor with placebo are highly consistent. The CONSENSUS study and both of the SOLVD trials showed that converting enzyme inhibition reduced the risk of pump failure but not of sudden death. Differences in classification in a blinded trial should be unbiased and can blur a difference, but they should not change the results if a difference is observed. In the SOLVD treatment and prevention trials, there was a small reduction (about 8%) in the risk of sudden death. From these data, you cannot conclude that there is no effect on sudden death. You can conclude only that the effect is much smaller than the effect on pump failure deaths. In the SOLVD trials there were 148 nonfatal cases of documented cardiac arrest, 74 each in the enalapril and placebo groups. In the SOLVD trials, enalapril had no effect on the risk of death that occurred without prior hospitalizations for heart failure. These three observations are congruent and indicate that angiotensin-converting enzyme inhibitors do not reduce the incidence of sudden death. The only logical explanation for the differences seen between the V-HeFT II study and all placebo-controlled trials of angiotensin-converting enzyme inhibitors was that the V-HeFT II study compared enalapril with active agents rather than placebo.

J. Cohn: I agree with your observations, but they are based on a self-fulfilling prophecy if 75% to 80% of your deaths are due to pump failure. Hence, it is impossible to detect an effect of a drug on sudden death if so few patients die suddenly. If half of the patients had died suddenly, you would have had a better chance of finding an effect on sudden death.

B. Pitt: In the SOLVD prevention trial, half of the cardiac deaths were sudden, and the small treatment benefit we observed was due to a reduction in death from progressive heart failure and not to a reduction in sudden death.

A. Katz: I would like to go back to mechanisms. If one looks for an explanation as to why angiotensin-converting enzyme inhibitors are more effective than other vasodilators, it is possible that these drugs act to prevent or to slow maladaptive growth processes. If converting enzyme inhibitors are acting as growth inhibitors, then one might predict that if they are given early in the course of myocardial infarction (that is, in the first few hours), when hypertrophy is probably more adaptive than maladaptive, one could see a detrimental effect rather than a beneficial effect of the drug. This has been reported from the Maastricht group (Schoemaker RG, Debets JJM, Struyker Boudier HAJ, Smits JFM. Delayed but not immediate therapy improves cardiac function in conscious rats following myocardial infarction. J Mol Cell Cardiol 1991;23:187–97). These data are supported clinically by the results of the CONSENSUS II study.

M. Pfeffer: When we first started our work on ventricular remodeling, we found that the results were similar if we intervened after 2 days or after 14 days but the results might have been different if we had intervened during the hyperacute phase of myocardial infarction. Dr. Cohn's study with nitroprusside showed that the effects of the drug were dependent on the timing of the intervention. Hence, I am concerned about producing hypotension on day 1 of an acute myocardial infarction, but I do not think this is related to the inhibition of hypertrophy.

E. Sonnenblick: I believe that during the acute phase of myocardial infarction (when there is early remodeling) there is a loss of cells resulting from the acute distension. That is why I think you need to intervene as early as possible and prevent as much of the remodeling as you can, because probably half of your remodeling takes place within the 1st week. I think we need to intervene earlier to prevent remodeling, slippage of cells and loss of cells and not just to prevent the expansion of the infarction.

M. Pfeffer: But then you have the risk of very early intervention, as Dr. Katz emphasized. I do not think we will understand the trade-off of benefit and risk in the early phases of an acute infarction until we carry out a trial that compares early and delayed intervention with an angiotensin-converting enzyme inhibitor. We are planning to carry out such a study that will compare the effects of a converting enzyme inhibitor administered on day 1 with those of a converting enzyme inhibitor administered on day 14 after an acute myocardial infarction. This trial will have an echocardiographic end point.

M. Packer: I am struck by the fact that no one has asked a question about Dr. Yusuf's provocative proposal that converting-enzyme inhibitors should be evaluated for their ability to prevent recurrent ischemic events in all patients who have had an acute myocardial infarction. This is an interesting idea, but I can foresee a problem. If aspirin attenuates the effects of converting enzyme inhibitors, how will we be able to show that converting enzyme inhibitors

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reduce the risk of reinfarction, because most of the patients receiving converting enzyme inhibitors are also receiving aspirin?

S. Yusuf: In my view, there is no basis for the claim that aspirin inhibits the effect of angiotensin-converting enzyme inhibitors. If we focus on the end points in the SOLVD trial where treatment appears to have a made difference (that is, pump failure and myocardial infarction), there is no evidence of an interaction. The interaction appears to be related to an unusual distribution of noncardiac deaths and I believe represents a statistical quirk. I would be interested in seeing what the SAVE trial shows, because 60% of the patients in that study were receiving aspirin.

M. Packer: Dr. Pfeffer, do we know if there was an interaction between aspirin and captopril in the SAVE trial?

M. Pfeffer: We do not know that yet.

M. Packer: We will await the results with interest. Is anyone thinking about carrying out a definitive secondary prevention trial with a converting enzyme inhibitor?

B. Pitt: There is one such trial in progress. The Quinapril Ischemic Event Trial (QUIET) is exploring the effect of angiotensin-converting enzyme inhibitors on ischemic events in patients with a preserved left ventricular ejection fraction who have recently undergone coronary angioplasty. Approximately 1,700 patients have been enrolled in the study and are being followed up for ischemic events. In a subset of 600 patients, serial angiograms are performed to look for angiographic evidence of disease progression.

J. Cohn: One provocative observation is that enalapril reduced the risk of recurrent ischemic events. However, in both the V-HeFT and the SOLVD treatment trials, enalapril tended to be more effective in patients with nonischemic cardiomyopathy than in those with ischemic heart disease, although the interaction was not quite significant. It raises the possibility that the benefit of angiotensin-converting enzyme inhibitors in patients with ischemic heart failure may be largely related to the reduction of ischemic events and that the drug may be acting by a different mechanism in patients with nonischemic heart disease.

M. Packer: Why did the SOLVD trial show a reduction in the risk of reinfarction with enalapril in patients who did not have coronary artery disease?

S. Yusuf: Many patients with nonischemic heart disease had long-standing hypertension and their average age was 60 years. Hence, some may have had silent coronary artery disease. Incidentally, were data on myocardial infarction collected in the V-HeFT II study?

J. Cohn: Yes, but the number of events was quite small.

G. Guyatt: I am impressed by the low proportion of people in the trials who were receiving aspirin and beta-blockers, because these drugs should have been indicated in most of the patients enrolled in these studies. It is wonderful to show effects in clinical trials, but unless physicians use drugs of established worth, these studies will not have much of an impact. Is there an explanation for the relatively low use of aspirin and beta-blockers in these trials?

M. Pfeffer: In the SAVE trial, ≈60% of the patients were receiving aspirin, another 15% were taking other antiplatelet drugs, 30% were prescribed coumadin at the time of enrollment into the study. In contrast, despite evidence of benefit, only one third of our patients were receiving a beta-blocker.

B. Pitt: In the SOLVD trial, a third of the patients with a low ejection fraction were receiving first-generation calcium channel blockers, although the available trial data indicate that this is not the right thing to do.

M. Packer: We would like to think that the investigators in the SOLVD, SAVE and V-HeFT trials would have faithfully translated the conclusions from earlier studies into clinical practice.