

## Rationale for Angiotensin Receptor Blockers in Congestive Heart Failure

*Based on a presentation by Alan H. Gradman, MD*

### *Presentation Summary*

With respect to heart failure treatment, current therapies have not offered the degree of reduction in heart failure progression that was expected. Specifically, angiotensin converting enzyme inhibitors tend to reduce heart failure progression for a limited time before seemingly losing any efficacy in this area. The possible reasons for this are explored.

Although angiotensin receptor blocking agents may provide better heart failure therapy because of more complete renin-angiotensin system blockade, clinical data so far has shown only that they are at least

equal to angiotensin converting enzyme inhibitors on several counts.

Until more studies with appropriate primary endpoints are completed involving each of these new agents in heart failure patients, the issue will not be solved. Several such studies are now underway. However, Alan H. Gradman, MD, cautions that angiotensin receptor blockers may prove to be inferior to their predecessors for heart failure because of their lack of bradykinin-increasing effects. There is also a strong possibility that a combination regimen including both drugs may prove to be the most beneficial.

**E**ven though angiotensin converting enzyme (ACE) inhibitors have been one of the great success stories in the treatment of heart failure, there is significant deterioration of effect on an ongoing basis. Patients tend to do well for 1 to 3 years and then they progress," explained Alan H. Gradman, MD, chief, division of cardiovascular disease, Western Pennsylvania Hospital, and clinical professor of medicine, University of Pittsburgh School of Medicine.

There are several possible reasons for heart failure progression despite ACE inhibition. One cause may be that ACE

inhibitors only provide partial suppression of the renin-angiotensin system. It is now established that enzymatic pathways other than ACE exist and are involved in angiotensin II production. In addition, experimental and clinical data indicate that chymase is the primary enzyme responsible for the production of angiotensin II in the myocardium and the coronary vasculature.<sup>1</sup>

Another reason may be reactivation of the system at some point during treatment. "Although the drugs provide an initial suppression of angiotensin II, the angiotensin II levels eventually rise back to baseline levels. This phenome-

non has been documented in hypertensive patients, and we can speculate that the same mechanism applies to heart failure," he said.<sup>2</sup>

Sympathetic activation is another possible reason for declining efficacy, and there are many other factors which can cause myocardial deterioration over time, some having nothing to do with the renin-angiotensin system. "The critical fact is that deterioration occurs with ACE inhibition, and it seems to be inexorable," Dr. Gradman said.

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— Alan H. Gradman, MD

### Angiotensin Receptor Blockers Show Promise

"The promise of angiotensin receptor blockers (ARBs) is that, unlike ACE inhibitors, they can block all of the angiotensin II at the receptor whether it is produced through the action of ACE or through other pathways," Dr. Gradman noted. It is on this basis that it has been theorized that ARBs may be superior to earlier agents in treating heart failure. But it is also possible that the drugs will prove to be inferior to ACE inhibitors. If elevated bradykinin levels are indeed beneficial to heart failure patients, ARBs may not be the best choice, he said.<sup>3</sup>

"Another point worth making is that so far there has been no indication that the effects seen with one ARB are necessarily the effects that will be seen with another ARB. Each individual agent will have to be evaluated on its own," Dr. Gradman said.

"The goals of treating heart failure are to improve functional capacity, improve the quality of life for these patients, and unquestionably, to improve survival. We are very early in the development of research using ARBs toward these goals."

Although clinical experience with ARBs in heart failure patients is limited at this point in time, there is some trial data on agents currently in use for hypertension that at least suggest that further investigation is warranted, he noted.

Another important pharmacological strategy that is starting to receive attention, again based on limited clinical trial evidence, is that a combination of an ARB and an ACE-inhibitor may result in more complete angiotensin II inhibition while preserving the postulated benefits of bradykinin, Dr. Gradman said. "We seem to get a better hemodynamic response in animal models by using combined treatment." Furthermore, recently published data substantiates this improved response to combination treatment in heart failure patients.<sup>4</sup>

### Clinical Data

Each of the four ARBs currently available have been studied in heart failure to some extent either in the United States or abroad, according to Dr. Gradman. The limited data available from these studies do suggest that ARBs have similar effects on hemodynamic parameters, exercise tolerance, and functional capacity when compared to ACE inhibitors.

For example, in the Evaluation of Losartan in the Elderly (ELITE) Study, 12-weeks of treatment with either drug showed dose-dependent reductions in mean arterial pressure and pulmonary capillary wedge pressure, as well as a modest increase in cardiac output.<sup>5</sup>

In another important study, exercise tolerance studies comparing losartan and candesartan cilexetil to enalapril showed no significant difference in exercise tolerance between treatment with the ACE inhibitor or one of the ARBs. Additionally, the study showed no dif-

ferences in symptomatic status or New York Heart Association heart failure class when the agents were compared.<sup>6</sup>

“However, the overriding clinical question relates to the relative impact of individual ARBs, ACE inhibitors, or a combination of both on patient survival,” Dr. Gradman pointed out. In the ELITE trial, patients were randomized to either losartan or captopril for 48 weeks of treatment and no differences between the drugs were observed as far as the primary endpoint, which was deterioration in renal function.

“Overall tolerability was better with losartan but this was mainly due to the absence of cough,” he said. Another notable finding was that total mortality among losartan-treated patients was reduced by 46% when compared to the ACE inhibitor, and as mentioned previously, the mortality reduction was mostly due to a decrease in sudden death (Figure 1).<sup>5</sup>

“However, ELITE was not sufficiently powered to reliably evaluate mortality. Therefore, a similar study with a larger sample size—ELITE II—has been designed and is underway in an attempt to answer mortality questions,” according to Dr. Gradman.

In the RESOLVD study, mortality at study termination was 6.1% for patients receiving candesartan cilexetil only, 8.7% in the combined treatment group, and 3.7% in the enalapril only group. “Interpretation of this data is problematic because of underdosing in several candesartan cilexetil subgroups, small sample sizes, and a lower mortality rate in the enalapril group than has been observed in other studies,” Dr. Gradman said (Figure 2).

**Future Directions**

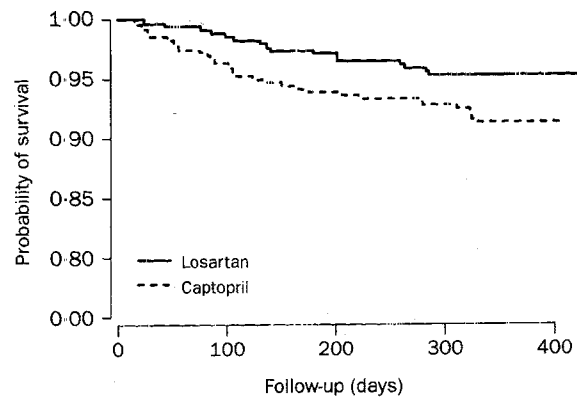
There is a definite need for more trials in order to evaluate the effects of the new ARB agents in heart failure, Dr. Gradman said. Several well-designed studies in addition to ELITE II are now underway that compare candesartan cilexetil to placebo in patients intolerant

of ACE inhibitors. The main endpoint will be tolerability.

Also, Valsartan Heart Failure Trial (Val-HeFT) is underway and will investigate the addition of 160 mg valsartan bid to the regimen in patients already being maintained on ACE-inhibitor therapy, according to Dr. Gradman.

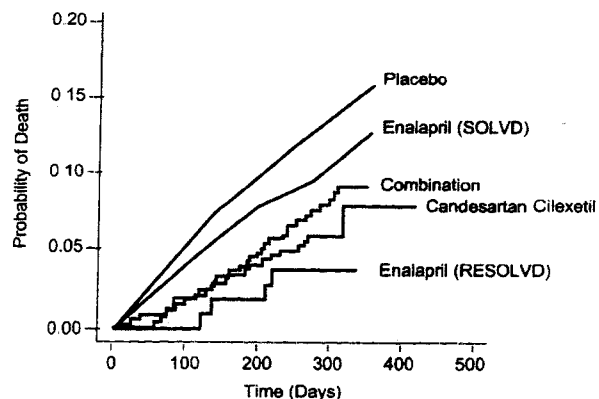
“It is anticipated that these trials will contribute greatly to our understanding of the role of specific ARBs in heart failure therapy,” he said.

**Figure 1. Reduced Mortality in Patients with CHF: Losartan vs Captopril (ELITE)**



Pitt et al *Lancet* 1997;349:747.

**Figure 2. RESOLVD vs SOLVD**



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