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Scientific Update™

Update on ACE inhibitors: The ATLAS and RESOLVD trials

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ATLAS

Many large clinical trials[1–3] have demonstrated that angiotensin converting enzyme inhibitors (ACEI) reduce morbidity and mortality in patients with congestive heart failure (CHF) and that these agents have become the first-line therapy for patients with CHF accompanied by systolic left ventricular dysfunction. In spite of the increasing use of ACEI in patients with CHF, most physicians usually prescribe much lower doses than those used in the clinical trials.

Several small trials,[4–6] including one reported in a previous issue of *Scientific Update*, have provided supportive evidence that patients derive more clinical benefits from high-dose than low-dose ACEI. The question as to whether low-dose ACEI is as effective as high-dose ACEI in reducing mortality remains unanswered.

To address this important clinical question, the Assessment of Treatment with Lisinopril and Survival (ATLAS) trial was conducted.

Design

The ATLAS trial was a randomized, double-blind, parallel group trial that compared the effects of low- and high-dose lisinopril on survival in patients with CHF. Entry criteria were left ventricular ejection fraction (EF) of <30% and New York Heart Association (NYHA) class II to IV symptoms.

Subjects first entered a 2- to 4-week open-label phase, and then were randomized to either of two regimens: 2.5–5.0 mg daily (low-dose group); or to 22.5–25.0 mg daily for two weeks, and then 32.5–35.0 mg daily (high-dose group). The initial plan was to follow 3,000 patients for three years. Several assumptions were made:

- annual mortality rate of 19% in the high-dose group
- 90% power to detect a 15% improvement in mortality for the low-dose group (22.4% annual mortality)
- complete followup with no "run-in" or run-out"
- 1,600 deaths anticipated

There were 3,583 patients entered in the open-label phase. The mean age of the entire cohort was 64 ± 10 years. 21% of the subjects were women. The proportions of patients with NYHA classes II, III, and IV symptoms were 16%, 77%, and 7%, respectively. The mean EF was 23%. The major etiology was ischemic heart disease (64%) followed by dilated cardiomyopathy (21%). Diabetics on treatment made up 20%. Over 80% of the patients were on ACEI prior to entry. There were 419 patients (11%) who withdrew prior to randomization, either for administrative reasons or because of events such as death or worsening CHF.

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Results

The first patient entered the ATLAS study in October 1992, with recruitment completed in June 1994. The study ended on September 15, 1997. Patients were followed from 39 to 52 months. The trial lasted for 54 months – longer than originally planned – for several reasons: The mortality was lower than anticipated, with less than 1,400 deaths (1,600 were projected). Furthermore, 19% of the low-dose group and 17.2% of the high-dose group took open-label ACEI after randomization. As a result, the median dose difference of lisinopril between the two groups decreased from 30 mg at the beginning of the study to 19 mg as the study evolved. Results of the primary outcome and selected secondary outcomes are shown in table 1.

A non-significant trend in favor of high-dose lisinopril was demonstrated in the primary outcome of all-cause mortality. There was a significant 12% reduction of the important secondary endpoints of combined all-cause mortality and all-cause hospitalizations. Other secondary endpoints that included hospitalization were also significantly in favor of high-dose lisinopril. Further analysis of other secondary endpoints that were not pre-specified attests to the internal consistency of the trend in favor of high-dose lisinopril; these include a significant reduction of all-cause mortality, of CHF hospitalization, and of the frequency of hospitalization for any reason. Among these endpoints, the most pronounced difference was the frequency of hospitalization due to CHF, where there was a 24.5% reduction due to high-dose lisinopril. The effect on mortality or combined mortality and hospitalization was not influenced by age, gender, etiology of CHF, ejection fraction, or NYHA class. There were no differences between the two groups in vascular events, myocardial infarction, hospitalization for unstable angina (odds ratio=0.918, p=0.374), or death and non-fatal myocardial infarction and hospitalization for unstable angina (odds ratio=0.915, p=0.077).

Overall, both high and low doses of lisinopril were similarly well-tolerated. As expected, there was a slightly higher incidence of hypotension/dizziness (26.5% versus 16.8%) and a worsening of renal function (26.5% versus 16.8%). However, adverse events resulting in withdrawal of study medications were similar (18% versus 17%). It is interesting that the increase in coughing was lower in the high-dose group (10.6% versus 13.2%).

The final blood-pressure difference between the two groups was 2 mm Hg, and the difference in creatinine was only 0.1%.

Table 1: ATLAS endpoints

	Low dose	High dose	Odds ratio (95% CI)	
Primary				
All-cause mortality	717/1596 (44.9%)	666/1568 (42.5%)	0.92 (0.82-1.03)	p=0.128
Secondary (ranked according to hierarchy)				
All-cause mortality + total hospitalizations	1339/1596 (83.9%)	1251/1568 (79.8%)	0.88 (0.82-0.96)	p=0.002
CVS mortality	641/1596 (40.2%)	583/1568 (37.2%)	0.90 (0.81-1.01)	p=0.073
All-cause mortality + CVS hospitalizations	1156/1596 (70.7%)	1080/1568 (66.9%)	0.92 (0.84-0.99)	p=0.036
All-cause mortality + CHF hospitalizations	946/1596 (60.4%)	864/1568 (55.1%)	0.86 (0.78-0.94)	p=0.001
Frequency of hospitalization				
Any reasons	4397	3819	—	p=0.021
CVS reasons	2923	2456	—	p=0.05
CHF reasons	1576	1199	—	p=0.002

Table 2: ACEI doses in four large clinical trials				
Trial	Year	Agent	Dose range	Median Dose
CONSENSUS	1987	Enalapril	2.5-40 mg	18.4 mg
VHeFT	1991	Enalapril	2.4-40 mg	15.0 mg
SOLVD	1991	Enalapril	2.5-20 mg	16.6 mg
AIRE	1993	Ramipril	5.0-10 mg	8.8 mg

Clinical implications

Although accurate information regarding international prescribing practices as regards doses of ACEI used in treating CHF are not readily available, it is the overall impression of clinical trialists and clinicians alike that such doses are lower than those in the clinical trials. To put this in perspective, table 2 lists the doses of ACEI employed in four large CHF survival trials.

Based on information obtained from the Food and Drug Administration in 1992, 40% of patients who were treated with enalapril for CHF were prescribed between 2.5 and 5 mg. The reason for this under-dosing is unclear, but it might be prompted in part out of concern over possible adverse drug reactions (e.g., first-dose hypotension and impaired renal function) and partly by a unfounded belief that low doses are as effective as high doses. Results of ATLAS strongly suggest that high-dose ACEI is superior to low-dose ACEI in preventing death and hospitalizations, while both high and low doses are well-tolerated. Whether low-dose ACEI is beneficial for patients with CHF remains unproven.

The results from ATLAS are also consistent with those of other small studies[4–6] that compared low- versus high-dose ACEI in CHF. The recently-completed NETWORK study, which compared the effects of 5, 10, and 20 mg of enalapril on mortality in patients with CHF, showed no difference in mortality with the three doses employed. However, the study was probably underpowered, since only 1,533 patients were randomized and the followup of six months was likely too short.

Pharmacoeconomics

Based on the results of ATLAS – a 12% reduction of composite death and hospitalization and a 24% reduction in the frequency of hospitalization – treatment with high-dose lisinopril will prevent 100,000 combined events of death and hospitalization and 250,000 hospitalizations due to CHF in the United States. Treating 1,000 patients for three years will prevent 395 hospitalizations from all causes and 234 hospitalizations from CHF. Expressed another way, treating 8 patients per year will prevent 1 hospitalization; treating 13 patients per year will prevent 1 hospitalization from CHF. In the United States, based on a drug cost of $30 per month and cost of $3,500 per hospitalization (the latter being a conservative estimate), the net saving for treating 1,000 patients could be $165,000 per year. The results of ATLAS might therefore have clinical as well as health-economics implications.

RESOLVD – Pilot Study

ACEI improve exercise tolerance and reduce mortality in CHF.[1-3] In patients with asymptomatic left ventricular (LV) dysfunction, ACEI also reduce the incidence of the development of clinically-overt CHF.[3] As a result, ACEI have now become the cornerstone of CHF therapy.

Evidence exists[7] of alternative enzymatic pathways of angiotensin-II (A-II) production within the myocardium, implying that ACEI may not completely block the formation of A-II. Angiotensin-II type-I (AT_1) receptor antagonists may provide a more complete blockade of the renin-angiotensin pathway. On the other hand, ACEI can influence other enzymatic pathways, including the augmentation of bradykinin and nitric oxide—qualities that might contribute to the beneficial effects of ACEI.[8] Accordingly, the idea of combined use of ACEI and AT_1 receptor antagonists is appealing, since the bradykinin-enhancing effects of ACEI are preserved while the alternative pathways of A-II generation are bypassed, thus allowing complete AT_1 blockade.

Design

The Randomized Evaluation of Strategies for Left Ventricular Dysfunction (RESOLVD) Study evaluated the impact of the AT_1 antagonist candesartan cilexetil versus the ACEI enalapril in patients with reduced LV function and clinical symptoms of CHF. After each patient had taken a 6-minute walk, investigators measured LV function, neurohormones, and quality of life (QOL).

Table 3: RESOLVD medication regimens				
		Low	Medium	High
Candesartan		4 mg o.d. n=111	8 mg o.d. n=108	16 mg o.d. n=108
Combination	Candesartan + Enalapril	4 mg o.d. 10 mg b.i.d. n=165	8 mg o.d. 10 mg b.i.d. n=167	—
Enalapril n=109	(standard dose) 10 mg b.i.d.			

RESOLVD was designed initially to be a pilot study, followed by a large-scale study. The pilot study was divided into two stages. Stage 1 evaluated the efficacy, safety, and tolerability parameters of candesartan (alone and in combination with enalapril) versus enalapril alone. Stage 2 was similar, but evaluation took place after the addition of a long-acting ß-adrenergic receptor blocker (metoprolol-CR) to the above regimens. The optimum dose found in the pilot study was then used in the subsequent large-scale study to determine the effects on mortality and hospitalizations.

The principal inclusion criteria were clinical CHF (New York Heart Association functional classes II to IV), LV ejection fraction <0.40, and a 6-minute walk distance of ≤500 m. After a three-week open-label run-in phase with candesartan (alone and in combination with enalapril) or enalapril alone, the patients were randomized to one of three regimens, as summarized in table 3.

For stage 1, outcome assessments were performed at week 18 and week 43. Patients who successfully completed 21 weeks of the RESOLVD study and had no contraindications to the use of ß-blockers were given the option to enter stage 2, in which the subjects were further randomized to metoprolol-CR 200 mg daily or placebo to determine the efficacy of metoprolol-CR in addition to candesartan/enalapril, using the same outcome parameters as in stage 1. Stage-2 outcome assessments were performed at baseline and 24 weeks. Stage-1 randomization began in February 1996 and RESOLVD was terminated in August 1997.

Results: Candesartan and/or enalapril

Data for clinical events collected up to week 43 for candesartan versus combination versus enalapril are shown in table 4.

Clinical and exercise parameters

In general, all the drug regimens were relatively well-tolerated. Over 85% of patients maintained the study medications, and discontinuation of drugs due to symptomatic hypotension was similar among the three groups at less than 1.2%. While there were no differences in NYHA class or QOL, patients treated with combination therapy (candesartan and enalapril) had a decrease in 6-minute walk as compared to an increase in the groups treated with either therapy alone.

Table 4: RESOLVD: Clinical events up to week 43				
	Candesartan	Combination	Enalapril	P value
	n=327	n=332	n=109	
Death	6.0%	8.7%	3.7%	0.148
CHF hospitalization	13.1%	9.3%	7.3%	0.136
Any hospitalization	26.3%	24.7%	22.9%	0.76
Death or CHF hospitalization	16.8%	17.2%	10.1%	0.189
Death or any hospitalization	29.1%	30.7%	24.8%	0.498

Table 5: RESOLVD: Clinical events up to week 22				
	Metoprolol-CR	Placebo	RR, 95% CI	P value
	n=215	n=211		
Death	3.7%	8.1%	0.46, 0.20–1.05	0.057
CHF hospitalization	8.4%	3.3%	2.52, 108–5.92	0.026
Any hospitalization	16.3%	17.1%	0.95, 0.02–1.46	0.828
Death or CHF hospitalization	10.7%	10.0%	1.07, 0.61–1.88	0.801
Death or any hospitalization	18.6%	20.9%	0.89, 0.61–1.31	0.560

Left ventricular function

At both 17 and 43 weeks, there was no difference in the increase from baseline in LV ejection fraction among the three groups. The increase in ejection fraction in the medium-dose combination was greatest, and it was significantly larger than in the enalapril-alone group. The increase in LV diastolic volume was significantly less in the combination regimens. A similar trend for systolic volume was also observed.

Neurohormonal parameters

At 17 and 43 weeks, plasma A-II level was increased in the candesartan-alone group, which was significantly different from a decline observed in the enalapril-alone group. When analyzed by dose, all three doses of candesartan increased A-II to a similar degree. Plasma aldosterone level was reduced by the combination but was unchanged in either of the single-drug groups at 17 weeks. The changes of pro-atrial natriuretic factor (proANF) were similar among the 3 groups, but at 43 weeks, plasma brain natriuretic peptide (BNP) level was reduced in the combination group and increased in both the single-drug groups.

Results: Metoprolol-CR versus placebo

Data for clinical events collected up to week 22 for metoprolol-CR versus placebo are shown in table 5.

Clinical and exercise parameters

In stage 2 of the study, the tolerability rate was also good (81.4% and 84.8% for metoprolol-CR and placebo group, respectively). There were no significant differences between the two groups in the 6-minute walk, NYHA class, or QOL measurements. As expected, there was a significantly more pronounced decline of heart rate (-6 beats/min) in the metoprolol-CR group compared to placebo (-1 beat/min) at 24 weeks.

Left ventricular function

Consistent with previous experience of ß-blockers in CHF, at 24 weeks the metoprolol-CR group had an increment in ejection fraction that was not observed in the placebo group. This improvement in ejection fraction was also associated with a smaller increase in diastolic volume.

Neurohormonal parameters

At 24 weeks, plasma renin activity and A-II level declined in the metoprolol-CR group and increased in the placebo group. Endothelin-1 level was unchanged in both groups, and norepinephrine level was reduced to a similar extent. It's interesting that both plasma proANF and BNP levels increased in the metoprolol-CR group and were unchanged in the placebo group.

Clinical events

As shown in table 4, there were no significant differences among the candesartan-alone, the combination, or the enalapril-alone groups with regards to any of the descriptors of mortality and morbidity. When the data were analyzed according to dose, there was no obvious systematic trend for dose-relationships in any of the clinical events within the candesartan-alone or the combination groups.

Table 5 shows that there were no significant differences between the metoprolol-CR and placebo

groups with the exception of CHF hospitalizations, which were higher in the metoprolol-CR group. It should, however, be emphasized that RESOLVD was a pilot study that was not designed or powered to assess clinical events. These data on clinical events should therefore be interpreted with extreme caution.

Conclusion

To date, there has been very little clinical experience with the combined use of ACEI and AT_1 receptor antagonists. In a recently-reported multicenter trial, the hemodynamic effects of the AT_1 receptor antagonist valsartan were examined in 40 patients with CHF on chronic ACEI therapy. When compared to placebo, valsartan produced a dose-dependent reduction in pulmonary capillary wedge pressure, and this effect was sustained after 28 days of therapy.[9] These findings indicate that AT_1 receptor blockade can augment the beneficial hemodynamic effects of chronic ACEI therapy. They are also consistent with the findings of the RESOLVD study that combination therapy exerts more pronounced effects on arterial blood pressure, and that it improves LV function and neurohormonal parameters to a greater degree than ACEI alone.

These superior effects of combination therapy have also been demonstrated recently in an experimental model of heart failure, in which combination therapy was superior to ACEI or AT_1 receptor antagonists in improving LV (whole organ) and isolated myocyte function.[10,11] Whether the additive hemodynamic and neurohormonal effects of combined use of ACEI and AT_1 receptor antagonists can be translated into a favorable effect on prognosis in patients with CHF is unclear. The ongoing international multicenter Valsartan Heart Failure Trial (Val-HeFT) is addressing this issue.

The beneficial effects of metoprolol-CR demonstrated in the RESOLVD study are consistent with those of other ß-blocker trials.[12] However, the findings that metoprolol-CR increased plasma proANF and BNP levels were unexpected. It is noteworthy that a population-based study presented at the same scientific meeting showed that patients on ß-blockade therapy had higher plasma ANP, BNP, and cGMP levels independent of anthropometric and cardiac structural parameters.[13] The composite findings suggest that ß-blockade therapy increases plasma natriuretic peptide levels. The mechanism for this effect is unclear, but it will undoubtedly provide fruitful ground for further basic and clinical research.

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