Comparison of Candesartan, Enalapril, and Their Combination in Congestive Heart Failure

Randomized Evaluation of Strategies for Left Ventricular Dysfunction (RESOLVD) Pilot Study

The RESOLVD Pilot Study Investigators

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Background—We investigated the effects of candesartan (an angiotensin II antagonist) alone, enalapril alone, and their combination on exercise tolerance, ventricular function, quality of life (QOL), neurohormone levels, and tolerability in congestive heart failure (CHF).

Methods and Results—Seven hundred sixty-eight patients in New York Heart Association functional class (NYHA-FC) II to IV with ejection fraction (EF), 0.40 and a 6-minute walk distance (6MWD), 500 m received either candesartan (4, 8, or 16 mg), candesartan (4 or 8 mg) plus 20 mg of enalapril, or 20 mg of enalapril for 43 weeks. There were no differences among groups with regard to 6MWD, NYHA-FC, or QOL. EF increased (P = NS) more with candesartan-plus-enalapril therapy (0.025 ± 0.004) than with candesartan alone (0.015 ± 0.004) or enalapril alone (0.015 ± 0.005). End-diastolic (EDV) and end-systolic (ESV) volumes increased less with combination therapy (EDV 27 ± 4 mL; ESV 18 ± 3 mL) or enalapril alone (EDV 23 ± 7 mL; ESV 14 ± 6 mL) than with candesartan alone (EDV 27 ± 4 mL; ESV 18 ± 3 mL or enalapril alone (EDV 23 ± 7 mL; ESV 14 ± 6 mL). Blood pressure decreased with combination therapy (6 ± 1/4 ± 1 mm Hg) compared with candesartan or enalapril alone (P < 0.05). Aldosterone decreased (P < 0.05) with combination therapy (23.2 ± 5.3 pg/mL) at 17 but not 43 weeks compared with candesartan (0.7 ± 7.8 pg/mL) or enalapril (20.8 ± 11.3 pg/mL). Brain natriuretic peptide decreased with combination therapy (5.8 ± 2.7 pmol/L; P < 0.01) compared with candesartan (4.4 ± 3.8 pmol/L) and enalapril alone (4.0 ± 5.0 pmol/L).

Conclusions—Candesartan alone was as effective, safe, and tolerable as enalapril. The combination of candesartan and enalapril was more beneficial for preventing left ventricular remodeling than either candesartan or enalapril alone.

Key Words: cardiac volume heart failure natriuretic peptides

Angiotensin-converting enzyme inhibitors (ACEIs) reduce angiotensin II (Ang II) levels, mortality, and morbidity in patients with heart failure (CHF).1,2 Despite ACEI treatment, Ang II increases via alternate pathways, while event rates remain high.1,4

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Ang II blockers (ARBs) might be superior to ACEIs by blocking Ang II from all sources without the side effects thought to be due to nonspecific actions of ACEIs.4 Evidence suggests that some benefits of ACEI treatment are derived from elevated levels of bradykinin.5 The combination of ACEI and ARB treatment may have additive actions.

The Randomized Evaluation of Strategies for Left Ventricular Dysfunction (RESOLVD) pilot study compared the effects of candesartan, enalapril, and their combination on exercise performance, ventricular function, quality of life (QOL), neurohormones, and tolerability.6 A secondary goal was to identify the optimal dose of candesartan for a larger study.

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Methods

Design
This was a multicenter, double-blind, randomized, parallel, placebo-controlled trial of candesartan alone, candesartan plus enalapril, or enalapril alone over 43 weeks. After 19 weeks, eligible patients were randomized to metoprolol or placebo in a partial factorial design; these data will be presented at a later date. No systematic interactions occurred across outcomes between the use of metoprolol with candesartan, candesartan plus enalapril, or enalapril; therefore, overall results are presented. The study received local institutional review board approval, and participants gave written informed consent.

Population
Patients with New York Heart Association functional class (NYHA-FC) II, III, or IV CHF, 6-minute walk distance (6MWD) $\leq 500$ m, and ejection fraction (EF) $\leq 0.40$ were eligible for the study; exclusion criteria were reported previously. Run-In/Eligibility
Run-in included three 1-week phases: enalapril 2.5 mg twice daily plus placebo candesartan; enalapril 2.5 mg twice daily plus candesartan 2 mg daily; and enalapril 2.5 mg twice daily plus placebo candesartan. The third week, duplicate 6MWD and neurohormone levels were measured, and radionuclide angiography was performed, (Figure 1).

Randomization/Follow-Up
Patients received either candesartan alone, candesartan plus enalapril, or enalapril alone. Candesartan patients were further randomized to 4, 8, or 16 mg daily. Combination-therapy patients received candesartan at either 4 mg plus enalapril 20 mg twice daily. Medications were blindly titrated upward over 4 to 6 weeks. Back-titration was allowed. Follow-ups were fortnightly during the up-titration period and less frequently thereafter.

End Points
End points included the change in 6MWD, EF, ventricular volumes, neurohormone levels, QOL, and NYHA-FC at weeks 17 or 18 and 43. Tolerance and adverse and clinical events were documented, with serious adverse events reviewed centrally.

6MWD tests were performed in duplicate. EF, end-diastolic (EDV), and end-systolic volumes (ESV) were measured by radionuclide angiography. Norepinephrine, epinephrine, renin, Ang II, aldosterone, endothelin-I, N-terminal pro–atrial natriuretic peptide (pro-ANP), and brain natriuretic peptide (BNP) were measured in 677 patients. The Minnesota Living With Heart Failure questionnaire was used to assess QOL.

Monitoring
An External Safety and Efficacy Monitoring Committee (ESEMC) reviewed accumulating data. Because this was a pilot study that was not powered to assess mortality and morbidity, there were no predetermined examinations of the data or boundaries for stopping the trial. On June 12, 1997, the ESEMC observed that mortality was 6.1% for the group receiving candesartan alone (4 mg 6.3%, 8 mg 6.5%, and 16 mg 5.5%), 8.7% for those receiving candesartan plus enalapril (4 mg plus 20 mg 6.1%; 8 mg plus 20 mg 11.4%), and 3.7% for those receiving enalapril alone (3-way group comparison $P=0.15$). CHF hospitalizations were 10.7% with candesartan alone (4 mg 8.1%, 8 mg 16.7%, and 16 mg 7.3%), 7.2% with candesartan plus enalapril (4 mg plus 20 mg 8.5%; 8 mg plus 20 mg 6.0%), and 3.7% with enalapril alone (3-way group comparison $P=0.048$). Mortality plus CHF hospitalization rates were 14.6% for candesartan alone (4 mg 13.5%, 8 mg 18.5%, and 16 mg 11.9%), 15.1% for candesartan plus enalapril (4 mg plus 20 mg 13.9%; 8 mg plus 20 mg 16.2%), and 6.4% for enalapril alone (3-way group comparison $P=0.058$).

The ESEMC voiced concern about the use of candesartan. The study executive committee reviewed these and additional RESOLVD data, as well as data from other ARB trials, and did not share the opinions of the ESEMC (data within RESOLVD were internally inconsistent, without a dose-related increase in adverse effects)
regarding the safety and efficacy of candesartan. The low event rate observed in patients in the enalapril arm of the study was much lower than previously noted, there was a lack of supportive data from trials of other ARBs, and unpublished candesartan data at Astra (the sponsor of the present study) were unconcerning. However, the study was terminated 6 weeks early. At that time, 695 patients (90%) had completed all visits, and for remaining patients, termination occurred within 10 days. Approximately 9% of patients had a shortened follow-up by a mean of 16 days, and 1% did not undergo final assessments.

Analyses
Repeated-measures ANOVA (ie, baseline, week 17 or 18, and week 43) was conducted across the 3 main groups, followed where appropriate by a post hoc Tukey test. Dose effect was tested secondarily (6 groups) by repeated-measures ANOVA. This analysis was exploratory, and therefore no adjustments to probability values were made for the 2 comparisons (3 groups and 6 groups).

The primary safety end point was the combination of adverse effects (renal dysfunction, symptomatic hypotension, or effects causing study medication discontinuation) and tolerability. Clinical events for patients taking enalapril, candesartan, and candesartan plus enalapril were analyzed by \( \chi^2 \) testing across 3 groups. Results are reported as mean±SE unless otherwise specified.

Results
Eight hundred ninety-nine patients entered the run-in phase, with 768 randomized. One protocol violation occurred, and the executive committee (blinded to treatment) excluded this patient.

Fewer patients in the candesartan and candesartan-plus-enalapril groups than in the enalapril group were receiving \( \beta \)-blockers; otherwise, the groups were similar (Table 1).

More than 90% of patients received ACEIs treatment before study entry. At 18 and 43 weeks, >80% of patients were receiving the target dose and >90% of patients were taking >80% of study medication, with no difference (\( P=\text{NS} \)) among groups.

Six-Minute Walk Distance
Baseline 6MWD was 379±5 m for candesartan, 386±5 m for candesartan plus enalapril, and 374±8 m for enalapril patients. There were no significant changes for candesartan (390±6 m), candesartan plus enalapril (385±6 m), or enalapril patients (387±11 m) over the 43-week study period.

Ventricular Function
Over 43 weeks, there was a trend toward an increase in EF for candesartan plus enalapril compared with candesartan or enalapril patients (\( P=\text{NS} \)) that was most prominent at 43 weeks with the higher dose of candesartan plus enalapril (Figure 2).

Baseline EDV was 260±7 mL for candesartan, 252±6 mL for candesartan plus enalapril, and 255±11 mL for enalapril patients. There was a difference among the groups (\( P<0.01 \)) in increase in EDV over time (\( P=0.007 \), with candesartan and enalapril patients showing increases (Figure 2A). There was no dose-by-time interaction for the 6 groups (\( P=0.12 \)) (Figure 2B).

Baseline ESV was 196±6 mL for candesartan, 188±6 mL for candesartan plus enalapril, and 192±10 mL for enalapril patients. There was a difference among the

### Table 1. Patient Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Candesartan (n=327)</th>
<th>Candesartan/Enalapril (n=332)</th>
<th>Enalapril (n=109)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age, y (SD)</td>
<td>62.8 (11.0)</td>
<td>63.5 (10.5)</td>
<td>62.82 (11.6)</td>
</tr>
<tr>
<td>Male/female</td>
<td>261 (80%)/66 (20%)</td>
<td>282 (85%)/50 (15%)</td>
<td>98 (90%)/11 (10%)</td>
</tr>
<tr>
<td>Class II/III/IV, %</td>
<td>62/36/2</td>
<td>66/33/1</td>
<td>56/40/4</td>
</tr>
<tr>
<td>Ejection fraction, %</td>
<td>0.27±0.11</td>
<td>0.28±0.11</td>
<td>0.27±0.09</td>
</tr>
<tr>
<td>6MWD, m±SD</td>
<td>367±82</td>
<td>368±84</td>
<td>358±91</td>
</tr>
<tr>
<td>Primary cause of CHF</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IHD</td>
<td>235 (72%)</td>
<td>232 (70%)</td>
<td>81 (74%)</td>
</tr>
<tr>
<td>IDC</td>
<td>56 (17%)</td>
<td>62 (19%)</td>
<td>14 (13%)</td>
</tr>
<tr>
<td>Other</td>
<td>33 (10%)</td>
<td>37 (11%)</td>
<td>13 (12%)</td>
</tr>
<tr>
<td>Drug therapy</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ACE-I</td>
<td>313 (96%)</td>
<td>313 (94%)</td>
<td>100 (92%)</td>
</tr>
<tr>
<td>Ang II antagonists</td>
<td>6 (2%)</td>
<td>3 (1%)</td>
<td>1 (1%)</td>
</tr>
<tr>
<td>Diuretics</td>
<td>230 (70%)</td>
<td>213 (64%)</td>
<td>86 (79%)</td>
</tr>
<tr>
<td>( \beta )-Blockers</td>
<td>47 (14%)*</td>
<td>44 (13%)*</td>
<td>25 (23%)</td>
</tr>
<tr>
<td>Nitrates</td>
<td>118 (36%)</td>
<td>133 (40%)</td>
<td>40 (37%)</td>
</tr>
<tr>
<td>Antiarrhythmics</td>
<td>45 (14%)</td>
<td>48 (15%)</td>
<td>19 (17%)</td>
</tr>
<tr>
<td>Calcium antagonists</td>
<td>38 (12%)</td>
<td>49 (15%)</td>
<td>15 (14%)</td>
</tr>
<tr>
<td>Aspirin</td>
<td>170 (52%)</td>
<td>187 (56%)</td>
<td>51 (47%)</td>
</tr>
<tr>
<td>Anticoagulants</td>
<td>104 (32%)</td>
<td>105 (32%)</td>
<td>33 (30%)</td>
</tr>
</tbody>
</table>

IHD indicates ischemic heart disease; IDC, idiopathic dilated cardiomyopathy.

*P<0.05.
groups \((P<0.05)\) in increase in ESV over time \((P=0.006)\), with candesartan and enalapril patients showing increases (Figure 2A). There was a dose effect: patients taking 8 mg of candesartan plus enalapril had a decline \((P<0.01)\) in ESV, whereas those taking 4 mg of candesartan plus enalapril had an intermediate effect \((P=\text{NS})\) compared with patients taking only enalapril, who showed an increase at 43 weeks (Figure 2B).

**Neurohormones**

Renin levels increased, with the smallest increase occurring with candesartan use (Table 2). Baseline Ang II was 30.5±1.2 pg/mL for candesartan, 28.5±1.3 pg/mL for candesartan plus enalapril, and 27.3±2.0 pg/mL for enalapril patients. Compared with enalapril use, Ang II increased markedly with candesartan use and less with combination therapy (Figure 3A). A dose effect was observed in candesartan and enalapril patients showing increases (Figure 2A). There was a dose effect: patients taking 8 mg of candesartan plus enalapril had a decline \((P<0.01)\) in ESV, whereas those taking 4 mg of candesartan plus enalapril had an intermediate effect \((P=\text{NS})\) compared with patients taking only enalapril, who showed an increase at 43 weeks (Figure 2B).
TABLE 2. Neurohormone Levels at Baseline and 17 and 43 Weeks After Randomization

<table>
<thead>
<tr>
<th>Neurohormone</th>
<th>Candesartan</th>
<th>Candesartan/Enalapril</th>
<th>Enalapril</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>BL</td>
<td>17 wk</td>
</tr>
<tr>
<td>Renin, pg/mL</td>
<td>43</td>
<td>100.0</td>
<td>132.6</td>
</tr>
<tr>
<td>±SE</td>
<td>16.5</td>
<td>18.3</td>
<td>20.5</td>
</tr>
<tr>
<td>Norepinephrine, pg/mL</td>
<td>283</td>
<td>478.1</td>
<td>438.3</td>
</tr>
<tr>
<td>±SE</td>
<td>15.2</td>
<td>15.6</td>
<td>13.1</td>
</tr>
<tr>
<td>Epinephrine, pg/mL</td>
<td>240</td>
<td>73.2</td>
<td>53.9</td>
</tr>
<tr>
<td>±SE</td>
<td>6.3</td>
<td>4.3</td>
<td>3.0</td>
</tr>
<tr>
<td>Pro-ANP, pmol/L</td>
<td>288</td>
<td>1507.3</td>
<td>1521.5‡</td>
</tr>
<tr>
<td>±SE</td>
<td>74.8</td>
<td>72.8</td>
<td>88.1</td>
</tr>
<tr>
<td>Endothelin, pg/mL</td>
<td>279</td>
<td>3.0</td>
<td>2.5</td>
</tr>
<tr>
<td>±SE</td>
<td>0.3</td>
<td>0.2</td>
<td>0.1</td>
</tr>
</tbody>
</table>

BL indicates baseline; n, number of patients per group at baseline.

*P<0.01 vs baseline; †P<0.05 vs baseline; ‡P<0.01 vs enalapril. Statistical analyses were performed on log-transformed values.

sartan patients, with 16 mg producing the greatest increase (Figure 3B). Baseline aldosterone was 129.8±6.5 pg/mL for candesartan, 114.3±6.1 pg/mL for candesartan plus enalapril, and 131.9±15.3 pg/mL for enalapril patients. The decrease in aldosterone at 17 weeks for patients taking both candesartan and enalapril was greater (P<0.01) than the decrease for those taking enalapril alone (Figure 3A). There were progressive decreases in plasma norepinephrine and epinephrine but no between-group differences (Table 2). Pro-ANP tended to increase primarily with candesartan and enalapril between 17 and 43 weeks (Table 2). Baseline BNP was 129.8±6.1 pg/mL for candesartan, 114.3±6.1 pg/mL for candesartan plus enalapril, and 49.9±5.6 pmol/L for enalapril patients. BNP (Figure 3A) decreased in patients taking candesartan plus enalapril but increased in those taking candesartan alone or enalapril alone (P=0.0002). The greatest effect compared with enalapril alone (P<0.01) was observed among patients taking 8 mg of candesartan plus enalapril (Figure 3B). The changes in endothelin levels were similar among the 3 groups (Table 2).

NYHA-FC and QOL
There were no significant differences in NYHA-FC or QOL at 18 or 43 weeks among the 3 groups.

Potassium and Creatinine Concentrations
Baseline potassium was 4.48±0.02 mmol/L for candesartan, 4.42±0.02 mmol/L for candesartan plus enalapril, and 4.40±0.04 mmol/L for enalapril patients. Compared with enalapril (17 weeks 0.00±0.05 mmol/L; 43 weeks −0.01±0.05 mmol/L), potassium decreased (P<0.05) with candesartan use (17 weeks −0.21±0.03 mmol/L; 43 weeks −0.23±0.03 mmol/L) and increased (P<0.05) with candesartan plus enalapril (17 weeks 0.13±0.03 mmol/L; 43 weeks 0.11±0.03 mmol/L). The proportion of patients with potassium levels ≥5.5 mmol/L was not significantly different among the treatment groups.

No significant differences in creatinine occurred among the 3 groups during follow-up.

Blood Pressure and Heart Rate
Baseline systolic blood pressure was 119±1 mm Hg with candesartan, 120±1 mm Hg with candesartan plus enalapril, and 121±2 mm Hg with enalapril. Baseline diastolic blood pressure was 72±1 mm Hg with candesartan, 73±1 mm Hg with candesartan plus enalapril, and 73±1 mm Hg with enalapril. Baseline heart rate was 76±1 bpm with candesartan, 75±1 bpm with candesartan plus enalapril, and 75±1 bpm with enalapril. Blood pressures declined similarly with candesartan or enalapril alone (Figure 4A) but more with candesartan plus enalapril throughout the study (P<0.01), without an increase in heart rate (Figure 4A).

Clinical Events
There were no significant differences in mortality, hospitalizations for CHF, or hospitalizations for any cause among the 3 groups (Table 3).

Discussion
RESOLVD is the first study to compare an ARB alone (candesartan) with the combination of an ARB plus an ACEI (enalapril) and an ACEI alone in CHF patients. There were 2 main findings. First, candesartan had an effect similar to that of enalapril on 6MWD, ventricular function, NYHA-FC, and QOL. Although there was an increase in Ang II with candesartan use, the impact on aldosterone was similar to that of enalapril. Both drugs appear to be equally well tolerated. Second, candesartan plus enalapril was well tolerated, as well as being most effective in prevention of left ventricular dilatation and suppression of aldosterone and BNP.

That candesartan and enalapril were observed to have similar effects is consistent with previous studies9 that observed no significant differences between losartan and enalapril in their effects on 6MWD, symptoms, laboratory evaluation, norepinephrine levels, or N-terminal ANP levels. The Evaluation of Losartan in the Elderly Study (ELITE)10 found no difference in renal function, death, hospitalization for CHF, or NYHA-FC between patients using losartan and those using captopril.
Importantly, our results demonstrated that candesartan plus enalapril may be more beneficial than either drug alone. Few data exist regarding such combination CHF therapy. Hamroff et al\textsuperscript{11} found that the addition of losartan to treatment for patients already taking an ACEI produced a 15 mm Hg decrease in systolic blood pressure with no impact on creatinine or potassium concentrations. In a pig model of rapid atrial pacing CHF, benazeprilat plus valsartan improved cardiac output, fractional shortening, pulmonary capillary wedge pressure, and wall stress, with declines in aldosterone more than by use of either drug alone.\textsuperscript{12}

Figure 3. A, Changes in Ang II, aldosterone, and BNP at 17 and 43 weeks for candesartan (■), candesartan plus enalapril (▲), and enalapril (▼). Statistical analyses performed on log-transformed values. *$P<0.01$, +$P<0.05$ compared with 0 weeks; #$P<0.01$ compared with enalapril. Aldosterone: candesartan $n=284$, candesartan plus enalapril $n=297$, enalapril $n=95$; Ang II: candesartan $n=285$, candesartan plus enalapril $n=298$, enalapril $n=94$; BNP: candesartan $n=245$, candesartan plus enalapril $n=251$, enalapril $n=84$. B, Changes in Ang II, aldosterone, and BNP at 17 and 43 weeks. Abbreviations as in Figure 2B. *$P<0.01$ compared with 0 weeks; #$P<0.01$ compared with enalapril. Statistical analyses performed on log-transformed values.
The lack of a significant increase in neurohormonal activation and the similarity of neurohormone concentrations in candesartan groups compared with enalapril groups in RESOLVD is important, because deterioration of clinical status may relate to neurohormonal activation. Baseline neurohormone measurements were obtained while patients were receiving enalapril 5 mg daily. Changes in neurohormones are consistent with other studies examining ACEIs or ARBs in CHF. These studies demonstrated similar effects on most measures, except Ang II. In the present study, candesartan plus enalapril produced the greatest decline in aldosterone at 17 and 43 weeks and the greatest increase in renin, which indicates more complete blockade of the renin-angiotensin-aldosterone system. This suggests the mechanisms by which ACEIs and ARBs block the renin-angiotensin-aldosterone system axis may be independent and complementary. The present study supports that the most favorable of the 6 drug doses was the combination of 8 mg of candesartan with 20 mg of enalapril.
Clinical Events

Death, CHF hospitalization, any hospitalization, and their clusters were not significantly different among the 3 groups. The mortality rate of 3.7% found in patients taking enalapril over 43 weeks was much lower than that found in patients taking enalapril in a large trial. In the present study, there were only 109 patients in the group taking enalapril alone, and therefore, there was considerable uncertainty concerning the mortality rates (95% CI of the rates varied from 0.2% to 7.2%). Two or 3 additional deaths in the enalapril group would nullify any apparent differences. Therefore, the RESOLVD data should not be viewed as being reliable in estimating the effects of candesartan or candesartan plus enalapril versus enalapril alone on clinical outcomes. The unreliability of small numbers is illustrated further by the conflicting results from 2 trials of losartan compared with an ACEI. In ELITE, there was a lower mortality rate (not a prespecified end point) with losartan than with captopril (4.8% versus 8.7%), whereas in another trial, this trend was reversed. These data suggest that results based on few clinical events should be interpreted with caution.

The surrogate outcomes used in the present trial are helpful in understanding the physiological mechanisms of the actions of the drug. They cannot reliably predict net clinical effects but do provide a useful guide for larger, more definitive studies evaluating the effects of ARBs on clinical outcomes. The coherence of our data on favorable neurohormonal levels and ventricular function with the use of candesartan plus enalapril suggests that ARBs may add to the effects of ACEIs in CHF.

Conclusions

The present study demonstrated that candesartan was as effective, safe, and tolerable as enalapril in patients with symptomatic CHF. The combination of candesartan and enalapril appears to be more beneficial for preventing left ventricular dilatation and suppressing neurohormonal activation than either candesartan or enalapril alone. It would therefore be appropriate to design larger trials to assess the effects of combination therapy on major clinical outcomes.

Appendix

Investigators and Committee Members

Clinical Centers


*Principal investigator.
Acknowledgments

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References


Comparison of Candesartan, Enalapril, and Their Combination in Congestive Heart Failure: Randomized Evaluation of Strategies for Left Ventricular Dysfunction
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