THERAPEUTICS

Candesartan reduced cardiovascular mortality and morbidity in chronic heart failure with low ejection fraction

Young JB, Dunlap ME, Pfeffer MA, et al. Mortality and morbidity reduction with candesartan in patients with chronic heart failure and left ventricular systolic dysfunction: results of the CHARM low-left ventricular ejection fraction trials. Circulation. 2004;110: 2618-26.

QUESTION

In patients with symptomatic chronic heart failure (CHF) and reduced left-ventricular ejection fraction (LVEF), does candesartan added to other effective therapies reduce cardiovascular mortality or CHF hospitalizations?

METHODS

Design: Subanalysis of 2 randomized place-bo-controlled trials, 1 adding candesartan in patients already taking angiotensin-converting enzyme (ACE) inhibitors (Candesartan in Heart Failure Assessment of Reduction in Mortality and morbidity [CHARM]-Added) and the other adding candesartan in patients who could not tolerate ACE inhibitors (CHARM–Alternative).

Allocation: Concealed.*

Blinding: Blinded (clinicians, patients, and outcome assessors).*

Follow-up period: Median 40 months.

Setting: 618 sites in 26 countries.

Patients: 4576 adults ≥ 18 years of age (mean age 65 y, 74% men) who had had symptomatic CHF for ≥ 4 weeks and LVEF $\leq 40\%$. Patients were receiving ACE inhibitors, β -blockers, diuretics, spironolactone, and/or digoxin.

Intervention: Candesartan (n = 2289), titrated as tolerated from 4 or 8 mg once daily to a goal of 32 mg once daily, or matching placebo (n = 2287).

Outcomes: A composite endpoint of cardiovascular death or CHF hospitalization. Secondary outcomes included cardiovascular death, CHF hospitalization, all-cause death, and adverse events.

Patient follow-up: 99.8% (intention-to-treat analysis).

MAIN RESULTS

Candesartan reduced cardiovascular deaths, CHF hospitalizations, and all-cause deaths, but increased adverse events (Table).

CONCLUSION

In patients with symptomatic chronic heart failure and reduced left-ventricular ejection fraction, candesartan reduced cardiovascular mortality, heart failure hospitalizations, and all-cause mortality, but increased adverse

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*See Glossary.

Candesartan vs placebo in chronic heart failure with left-ventricular systolic dysfunction

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Outcomes at median 40 mo	Candesartan	Placebo	Hazard ratio (95% CI)	RRR (CI)	NNT (CI)
CV death or CHF hospitalization	36%	41%	0.82 (0.74 to 0.90)	14% (8 to 21)	18 (12 to 32)
CV death	23%	26%	0.84 (0.75 to 0.95)	14% (4 to 22)	28 (18 to 90)
CHF hospitalization	23%	28%	0.76 (0.68 to 0.85)	21% (13 to 29)	17 (13 to 28)
All-cause death	28%	31%	0.88 (0.79 to 0.98)	10% (2 to 18)	32 (18 to 195)
				RRI (CI)	NNH (CI)
Discontinuation of study drug because of adverse events	23%	19%		23% (10 to 38)	24 (16 to 52)
Discontinuation of study drug because of creatinine increase	7%	3.5%		103% (56 to 163)	28 (21 to 43)
Discontinuation of study drug because of hyperkalemia	3%	0.5%		460% (202 to 938)	44 (33 to 62)

 \dagger CV = cardiovascular; CHF = chronic heart failure. Other abbreviations defined in Glossary; RRR, RRI, NNT, NNH, and CI calculated from data in article

COMMENTARY

The perils of overinterpreting subgroup analyses are well-known. The study by Young and colleagues combining CHARM-Added and CHARM-Alternative and examining only patients who had CHF with systolic dysfunction is better considered a prespecified individual patient data meta-analysis. It extends our knowledge of how best to treat these high-risk patients.

In patients who are relatively undertreated, adding the angiotensin II type 1–receptor blocker (ARB) candesartan led to important reductions in morbidity and mortality. These benefits accrued to all clinical and pharmacotherapy subgroups examined. The findings suggest that, in this setting, ARBs and ACE inhibitors are safe, and except for adverse effects of cough and angioedema associated with ACE inhibitors, have the same reversible adverse effects, such as hypotension, hyperkalemia, and renal failure. Finally, this study lays to rest concerns raised about harms associated with "maximal" neurohormonal blockade (i.e., ACE inhibitor plus β -blocker plus valsartan) (1).

There are 3 things this study does not tell us. First, to what extent would the reported absolute *incremental* benefits of adding candesartan be diminished if all patients had been treated with optimal therapy with other treatments? (1) It is time that trialists considered a prerandomization run-in period during which all standard treatments associated with mortality benefits are optimized. Second, how should tangible benefits (e.g., mortality reduction) be balanced against nontrivial adverse effects (e.g., reversible hypotension or renal failure)? Third, how many of the available drugs should be used and in what order?

For now, we should ensure that as many patients with CHF as possible are on reasonable doses of ACE inhibitors (rather than ARBs because of their track record of safety, efficacy, effectiveness, and lower costs) and β -blockers first and then attempt to add aldosterone blockers and ARBs.

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Reference

1. Majumdar SR, McAlister FA, Cree M, et al. Clin Ther. 2004;26:694-703.