Review: Angiotensin II receptor blocker plus angiotensin-converting enzyme inhibitor increases risk for adverse effects

Phillips CO, Kashani A, Ko DK, Francis G, Krumholz HM. **Adverse effects of combination angiotensin II receptor blockers plus angiotensin-converting enzyme inhibitors for left ventricular dysfunction: a quantitative review of data from randomized clinical trials.** Arch Intern Med. 2007;167:1930-6.

Clinical impact ratings: GIM/FP/GP ★★★★★★☆ Hospitalists ★★★★★★☆ Cardiology ★★★★★★☆

QUESTION

In patients with symptomatic left ventricular (LV) dysfunction, does the combination of an angiotensin II receptor blocker (ARB) and an angiotensin-converting enzyme inhibitor (ACE-I) increase risk for adverse effects more than standard therapy?

METHODS

Data sources: MEDLINE and EMBASE/Excerpta Medica (to December 2006), Cochrane Library, National Institutes of Health Clinical Trials and US Food and Drug Administration Web sites, and reference lists.

Study selection and assessment: Randomized controlled trials (RCTs) with ≥ 500 patients that compared the combination of ARB and ACE-I with standard therapy that included ACE-I for LV dysfunction, had ≥ 3 months of follow-up, and reported adverse effects. 4 RCTs met the selection criteria: 3 RCTs (n = 7633, mean age 63 y, 82% men) of patients with chronic heart failure (CHF) and 1 RCT (n = 9794, mean age 65 y, 69% men) of patients with acute myocardial infarction (AMI) and symptomatic LV dysfunction. Mean duration of follow-up was 25 months. Quality assessment of individual trials was done using the 5-point Jadad scale. Study quality was high (median Jadad score 4).

Outcomes: Medication discontinuation because of adverse effects, worsening renal function (increase in serum creatinine level > 0.5 mg/dL [44 µmol/L]), hyperkalemia (serum potassium level >5.5 mEq/L [5.5 mmol/L]), and symptomatic hypotension.

MAIN RESULTS

The combination of ARB and ACE-I was associated with increased risks for adverse effects in both patient groups (Table).

CONCLUSION

In patients with chronic heart failure or acute myocardial infarction with symptomatic left ventricular dysfunction, the combination of an angiotensin II receptor blocker and an angiotensin-converting enzyme inhibitor (ACE-I) increases risk for adverse effects more than standard therapy that includes an ACE-I.

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ARB plus ACE-I vs standard therapy that includes ACE-I in patients with CHF or AMI with symptomatic left ventricular dysfunction*

Outcomes at mean 25 mo	Patient group	Number of trials (n)	Weighted event rates		RRI (95% CI)	NNH (CI)
			ARB + ACE-I	Standard therapy		
Medication discontinuation because of adverse effects	CHF	2 (7192)	15%	11%	38% (22 to 55)	25 (17 to 42)
	AMI	1 (9794)	9.0%	7.6%	17% (3 to 34)	76 (42 to 427)
Worsening renal function	CHF	3 (7633)	3.2%	1.5%	117% (59 to 197)	58 (35 to 114)
	AMI	1 (9794)	4.7%	3.0%	58% (29 to 93)	58 (40 to 103)
Hyperkalemia	CHF	1 (2548)	3.4%	0.7%	387% (143 to 881)	37 (26 to 59)
	AMI	1 (9794)	1.2%	0.9%	33% (–10 to 97)	Not significant
Symptomatic hypotension	CHF	3 (7633)	2.4%	1.6%	50% (9 to 107)	124 (58 to 686)
	AMI	1 (9794)	18%	12%	53% (39 to 68)	17 (14 to 21)

*ACE-I = angiotensin-converting enzyme inhibitor; AMI = acute myocardial infarction; ARB = angiotensin II receptor blocker; CHF = chronic heart failure; other abbreviations defined in Glossary. Weighted event rates, RRI, NNH, and CI calculated from data in article using a fixed-effects model.

COMMENTARY

Phillips and colleagues combined data from 4 trials to show that adding an ARB to an ACE-I causes known side effects of inhibition of the renin–angiotensin system. It is unclear why the trial involving an AMI population (Valsartan in Acute Myocardial Infarction Trial [VALIANT]) was included in this review, because that trial had already concluded that, in the AMI population, adding ARB to ACE-I provides no further benefit and has side effects. For the CHF population, the authors did not clearly describe some study comparisons (in CHARM-Added, candesartan was added to a variety of ACE-Is, not just enalapril, and in both CHARM-Added and Valsartan Heart Failure Trial [Val-HeFT], ARB + ACE-I was compared with placebo + ACE-I, not just placebo).

The safety outcomes have already been reported for the 3 CHF trials, and the 2 large trials each showed overall benefits of reduction in the composite of death or HF hospitalization by adding ARB (vs placebo) to background ACE-I. CHARM-Added, in which all patients were on background ACE-I at relatively high doses, showed a 15% relative risk reduction in cardiovascular death or HF hospitalization (P = 0.01) and a reduction in cardiovascular death alone (P = 0.03) (1). Quality of life was improved in both CHARM and Val-HeFT.

Side effects, including hyperkalemia (2), call for careful monitoring, including checking electrolytes periodically and within 2 weeks of any dose titration, as was done in the trials. This vigilance is especially important because patients in trials receive more careful monitoring than in practice; thus, serious side effects may have been underestimated.

In summary, this review was not very helpful because it did not address the key issue for deciding whether a treatment should be used: Is the balance of risk and benefit favorable? The trials of adding ARB to ACE-I in HF show that it is favorable, as long as treatment is accompanied by careful monitoring.

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References

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