

Review: Angiotensin-receptor blockers do not reduce mortality or hospitalization rates in heart failure

Jong P, Demers C, McKelvie RS, Liu PP. Angiotensin receptor blockers in heart failure: meta-analysis of randomized controlled trials. *J Am Coll Cardiol*. 2002 Feb 6;39:463-70.

QUESTION

In patients with heart failure (HF), do angiotensin-receptor blockers (ARBs) reduce mortality and hospitalization rates?

DATA SOURCES

Studies were identified by searching MEDLINE, EMBASE/Excerpta Medica, Biological Abstracts, International Pharmaceutical Abstracts, Cochrane Controlled Trials Database, McMaster Cardiovascular Randomized Clinical Trial Registry, and Science Citation Index up to May 2001.

STUDY SELECTION

Studies were selected if they were randomized controlled trials with blinding and at least 4 weeks of follow-up that compared ARBs with either placebo or angiotensin-converting enzyme inhibitors (ACEIs) in patients with New York Heart Association functional class II to IV HF and if they reported on mortality and hospitalization rates. Studies reported in non-peer-reviewed journals were excluded.

DATA EXTRACTION

Data were extracted independently by 2 reviewers on patient characteristics, drug type and dose, mean follow-up, and outcomes.

MAIN RESULTS

17 trials (12 469 patients) met the selection criteria. All trials reported mortality rates; 1674 patients died. The ARB and control groups did not differ for mortality or hospitalization rates (reported in 6 trials) (Table). None of the stratified analyses (ARBs vs placebo [7 trials], ARBs vs ACEIs [6 trials], ARBs and ACEIs in combination vs ACEIs alone [6 trials]) reached statistical significance for either outcome except for the combination of ARBs and ACEIs, which showed a benefit for reducing the hospitalization rate over ACEIs alone (Table). The review had 90% power to detect an absolute risk reduction of 2.0% in all-cause mortality and a

2.4% reduction in the hospitalization rate with a type-1 error rate of 5%.

CONCLUSION

In patients with heart failure, angiotensin-receptor blockers do not reduce mortality hospitalization rates more than do angiotensin-converting enzyme inhibitors or placebo.

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Angiotensin receptor blockers (ARBs) vs placebo or angiotensin-converting enzyme inhibitors (ACEIs) in heart failure at 4 weeks to 1.5 years*

Outcomes	ARBs	ACEIs or placebo	RRR (95% CI)	NNT (CI)
Death	13%	15%	4% (-19 to 22)	Not significant
Hospitalization	14%	17%	12% (-5 to 27)	Not significant
	ARBs and ACEIs	ACEIs		
Hospitalization	13%	17%	22% (12 to 32)	26 (19 to 49)

*Abbreviations defined in Glossary; RRR, NNT, and CI calculated from data in article by using a random effects model.

COMMENTARY

The initial success of ACEIs for reducing mortality in patients with HF caused by left ventricular systolic dysfunction has led to the search for even better formulations. The hypothesis that a better result could be obtained by agents that directly and specifically or more completely antagonize angiotensin II was appealing. How ACEIs actually reduce mortality is not fully understood. What if the other seemingly minor pathways blocked by ACEIs, which were theoretically responsible for their side effects, were an important component of their benefit?

The Evaluation of Losartan in the Elderly study (ELITE)-II (1) was designed to assess mortality differences between the ARB losartan and the ACEI captopril. Some commentators have been overly generous in suggesting that ELITE-II indicated that an ARB was equivalent to an ACEI. However, the data showed trends favoring the ACEI. So the best that could be said from ELITE-II was that an ARB was "not superior to" an ACEI.

Would patients benefit from having both types of medication? In the Valsartan Heart Failure Trial (Val-HeFT) (2), an ARB was added to current therapy, which resulted in no change in overall mortality and a reduction in the number of hospitalizations caused by HF. However, benefit was markedly influenced by concomitant therapy. There was benefit when an ARB was added if patients were not receiving an ACEI or β -blocker, modest benefit if they were receiving an ACEI or a

β -blocker but not both, and increased death and hospitalization if they were already receiving both an ACEI and a β -blocker.

The ELITE-II and Val-HeFT data are important here because their inclusion is the primary difference between the present meta-analysis by Jong and colleagues and previous ones. Either of these trials dwarfs all previous trials combined. Since ELITE-II was done, practice guidelines have appropriately placed ACEIs as first-line therapy, with ARBs to be substituted if "intolerance" or "contraindication" exists. However, intolerance is most often mild, ameliorated with time, and often overcome when the patient understands how pivotal the ACEI is for their condition. ACEIs and ARBs have similar contraindications and adverse renal effects.

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References

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