

ACE inhibitors reduced cardiovascular events and all-cause mortality in elderly persons with hypertension

Wing LM, Reid CM, Ryan P, et al. A comparison of outcomes with angiotensin-converting-enzyme inhibitors and diuretics for hypertension in the elderly. *N Engl J Med*. 2003;348:583-92.

QUESTION

In older persons with hypertension, is a regimen based on angiotensin-converting enzyme (ACE) inhibitors more effective than one based on diuretics for reducing cardiovascular events and all-cause mortality?

DESIGN

Randomized (allocation concealed*), blinded (outcome assessors),* controlled trial with median follow-up of 4.1 years (Second Australian National Blood Pressure Study [ANBP2]).

SETTING

1594 family medical practices in Australia.

PATIENTS

6083 patients who were 65 to 84 years of age (mean age 72 y, 51% women) without recent (previous 6 mo) cardiovascular events and had hypertension (defined as systolic blood pressure \geq 160 mm Hg or diastolic blood pressure \geq 90 mm Hg with systolic blood pressure \geq 140). Exclusion criteria included any life-threatening illness, a plasma creatinine concentration $>$ 221 μ mol/L, malignant hypertension, and dementia. Follow-up was 100%.

INTERVENTION

Patients were allocated to a treatment regimen based on ACE inhibitors ($n = 3044$) or diuretics ($n = 3039$) as the initial recommended therapeutic agents. However, the choice of the specific agent and dose was made by the family practitioners.

MAIN OUTCOME MEASURES

The primary outcome was a composite of all cardiovascular events and all-cause mortality.

MAIN RESULTS

Analysis was by intention to treat. At the end of the study, 58% of patients randomly assigned to the ACE-inhibitor group and 62% of those assigned to the diuretics group were still receiving the assigned treatment. At 5 years, blood pressure had decreased by 26/12 mm Hg from baseline in both groups. The rate of the composite outcome was

lower in patients who were allocated to the ACE-inhibitor group than in those who were allocated to the diuretics group ($P = 0.05$) (Table).

CONCLUSION

In older persons with hypertension, a treatment regimen based on angiotensin-converting enzyme inhibitors was more effective than one based on diuretics for reducing a composite outcome of all cardiovascular events and all-cause mortality.

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*See Glossary.

Angiotensin-converting enzyme (ACE) inhibitors vs diuretics in older persons with hypertension at 5 years†

Outcome	Rate per 1000 patient-years		Hazard ratio (95% CI)	NNT (CI)‡
	ACE inhibitors	Diuretics		
Composite outcome	56.1	59.8	0.89 (0.79 to 1.00)	32 (18 to 445)

†Composite outcome = all cardiovascular events and all-cause mortality. Abbreviations defined in Glossary; NNT and CI provided by author.

‡Number needed to treat with an ACE inhibitor–based regimen for 5 years to prevent 1 additional first cardiovascular event or death within the first 5 years after treatment began.

COMMENTARY

The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) (1) is considered by some to be one of the most important hypertension studies of all time. This large and well-designed study showed that essentially no differences existed in outcomes among patients randomized to regimens initiated with the use of ACE inhibitors, calcium-channel blockers, and diuretics. However, ANBP2, published a few months later, found that ACE inhibitors provided an “outcome advantage over a diuretic-based regimen,” leading one renowned hypertension expert to bemoan, “What are we to believe?” (2).

Some definite differences exist between the studies. Less than 50% of the ALLHAT population was white, compared with 95% of the ANBP2 population. If ACE inhibitors have more positive effects on whites than on nonwhites, independent of blood pressure–lowering effects, this could affect the results. There were also differences in baseline risks. Both of these studies were very large, and very large studies tend to find statistically significant differences between treatments that actually have very little clinical difference. In the study by Wing and colleagues, the difference in the rate of events was small (i.e., 3.7 events per 1000 patient-years), the rate of abandoning allocated therapy was large (about 40% in each group), and the upper limit of the number needed to treat was $>$ 400 patients. Thus, the difference is not very clinically important, despite the statistical significance.

The emphasis on relatively minor improvement in outcomes by diuretics in ALLHAT and by ACE inhibitors in the current study tends to obscure the most important result: that there are essentially no clinically important differences between these therapies, and that in uncomplicated patients, diuretics as a first-line choice are likely to provide an excellent (and unsurpassed) outcome. Given the poor awareness and management of hypertension (3), our efforts would best be used to improve the latter as opposed to the tedious arguments about the superiority of one drug over another.

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References

1. Major outcomes in high-risk hypertensive patients randomized to angiotensin-converting enzyme inhibitor or calcium channel blocker vs diuretic: The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT). *JAMA*. 2002;288:2981-97.
2. Frohlich ED. Treating hypertension—what are we to believe? [Editorial]. *N Engl J Med*. 2003;348:639-41.
3. Moser M. No surprises in blood pressure awareness study findings: we can do a better job [Editorial]. *Arch Intern Med*. 2003;163:654-6.