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


QUESTION: In older people 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
Randomised (allocation concealed*), blinded (outcome assessors),* controlled trial with median follow up of 4.1 years (Second Australian National Blood Pressure Study [ANBP2]).

Setting
1394 family medical practices in Australia.

Patients
6083 patients who were 65–84 years of age (mean age 72 y; 51% women) without recent (previous 6 mo) cardiovascular events and had hypertension (defined as systolic blood pressure ≥ 160 mm Hg or diastolic blood pressure ≥ 90 mm Hg with systolic blood pressure ≥ 140 mm Hg). Exclusion criteria included any life threatening illness, a plasma creatinine concentration > 221 μmol/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 inhibitors group than in those who were allocated to the diuretics group (p=0.05) (table).

Conclusion
In older people 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.

*See glossary.

COMMENTARY
The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) 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 randomised 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 non-whites, independent of blood pressure lowering effects, this could affect the results. Baseline risks also differed. 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 et al, the difference in the rate of events was small (ie, 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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1 Major outcomes in high-risk hypertensive patients randomised to angiotensin converting enzyme inhibitors or calcium channel blockers or diuretics: The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT). JAMA 2002;288:2081–97.
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.