

## THERAPEUTICS

## Review: Low-dose thiazides are the most effective first-line drugs for hypertension

Wright JM, Lee CH, Chambers GK. Systematic review of antihypertensive therapies: does the evidence assist in choosing a first-line drug? *CMAJ*. 1999 July 13;161:25-32.

### QUESTION

In patients with hypertension, which first-line drugs are effective for reducing death and cardiovascular events?

### DATA SOURCES

Studies were identified by searching MEDLINE (1966 to 1997), the Cochrane Library (1998 issue 2), and references of previous meta-analyses (1980 to 1997).

### STUDY SELECTION

Studies were selected if patients had systolic blood pressure  $\geq$  160 mm Hg or diastolic blood pressure  $\geq$  90 mm Hg; random allocation was used; a first-line antihypertensive drug was compared with another first-line drug or no treatment (including placebo); group baseline characteristics were reported; end points were defined;  $\geq$  1-year of follow-up was reported; and  $>$  70% of patients were receiving the study drug after 1 year. Studies were excluded if antihypertensive drugs were used for indications other than hypertension.

### DATA EXTRACTION

2 reviewers independently extracted data on patients, study duration, treatment, outcomes (death, stroke, coronary artery disease [CAD], and total cardiovascular events), and withdrawals because of adverse effects.

### MAIN RESULTS

23 studies (50 853 patients) met the inclusion criteria. Sample sizes ranged from 87 to 17 354 patients. In meta-analyses of drug–drug comparisons, no differences existed in death, stroke, CAD, or total cardiovascular events. Fewer withdrawals because of adverse effects occurred with thiazides than with  $\beta$ -blockers and in 1 trial with a calcium-channel blocker than with an angiotensin-converting enzyme (ACE) inhibitor (Table). In comparisons of drugs with no treatment, low-dose thiazides reduced death, and thiazides (all doses) and a calcium-channel blocker reduced stroke and total cardiovascular

events; only low-dose thiazides reduced CAD (Table).

### CONCLUSION

In patients with hypertension, low-dose thiazides are effective for reducing death, stroke, and coronary artery disease.

*Sources of funding: British Columbia Ministry of Health and the University of British Columbia.*

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### Effectiveness of first-line antihypertensive drugs for hypertension at up to 10 years\*

Comparison	Number of studies	Outcomes	Pooled RRR (95% CI)
Thiazides vs $\beta$ -blockers	5	Withdrawals because of adverse effects	31% (24 to 37)
Low-dose thiazides vs no treatment	5	Death Stroke Coronary artery disease Cardiovascular events	11% (1 to 19) 34% (21 to 44) 29% (16 to 40) 32% (25 to 38)
High-dose thiazides vs no treatment	11	Stroke Cardiovascular events	53% (39 to 63) 28% (18 to 37)
Calcium-channel blockers vs no treatment	1	Stroke Cardiovascular events	39% (13 to 57)† 39% (13 to 43)†
<b>RRR (CI)</b>			
ACE inhibitors vs calcium-channel blockers	1	Withdrawals because of adverse effects	231% (119 to 400)

\*ACE = angiotensin-converting enzyme. Other abbreviations defined in Glossary.

†Not pooled.

### COMMENTARY

Many large studies have shown that low-dose thiazide diuretics are efficacious and efficient in treating hypertension. Several national guidelines, including the U.S. Joint National Committee on the Prevention, Detection, and Evaluation and Treatment of Hypertension (1), have recommended thiazides as first-line antihypertensive therapy. Yet in practice, use of thiazides lags far behind the newer antihypertensive drugs, even though the effectiveness of these has been less well shown.

Unfortunately, few direct comparisons have been done among different classes of antihypertensive drugs. Those comparisons that have been done were limited to 2 classes of drugs in any 1 study, usually between  $\beta$ -blockers and thiazides. A comparison of several classes of drugs is now under way in the Antihypertensive and Lipid Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) study (2). It is designed to compare the mortality and cardiovascular outcomes of a

relatively high-risk group of patients with hypertension treated with either a thiazide, a calcium-channel blocker, an ACE inhibitor, or an  $\alpha$ -blocker. This large study with 42 451 patients is partially completed, and final results are expected in 2 to 3 years.

What should clinicians do until then? As concluded in this and other systematic reviews (using somewhat different methods), low-dose thiazides should be the first line of treatment for hypertension. Such therapy reduces not only risk for stroke but also other cardiovascular morbidity and mortality. Thiazides are inexpensive drugs with the strongest evidence for effectiveness from hypertension studies.

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### References

1. *Arch Intern Med*. 1997;157:2413-46.
2. *Davis BR, Cutler JA, Gordon DJ, et al. Am J Hypertens*. 1996;9:342-60.