

# Review: Low-dose diuretics are the best first-line antihypertensive therapy

Psaty BM, Lumley T, Furberg CD, et al. Health outcomes associated with various antihypertensive therapies used as first-line agents: a network meta-analysis. *JAMA*. 2003;289:2534-44.

## QUESTION

In patients with hypertension, how do low-dose diuretics compare with other antihypertensive agents as first-line therapy in preventing major cardiovascular disease (CVD) endpoints?

## DATA SOURCES

Studies were identified by searching MEDLINE (1995 to 2002), previous meta-analyses, and journal reviews.

## STUDY SELECTION

Studies were selected if they were randomized controlled trials evaluating major CVD endpoints in hypertensive patients treated with placebo, diuretics,  $\beta$ -blockers, calcium-channel blockers, angiotensin-converting enzyme (ACE) inhibitors, angiotensin-receptor blockers, or  $\alpha$ -blockers.

## DATA EXTRACTION

2 investigators independently extracted data on patients, interventions, and outcomes. Outcomes were coronary heart disease (CHD) (fatal and nonfatal myocardial infarction and CHD death); fatal and nonfatal stroke; fatal and nonfatal congestive heart failure (CHF); CVD events (CHD, stroke, CHF, and other CVD mortality); and total mortality.

## MAIN RESULTS

Analysis was done using network meta-analysis, which combined all available compar-

isons both within and between trials. 42 RCTs ( $n = 192\,478$ ) with mean follow-up of 3 to 4 years met the selection criteria. Compared with placebo, untreated control, or usual care, any active treatment reduced the risk for major outcomes. Low-dose diuretics (usually 12.5 to 25 mg/d of chlorthalidone or hydrochlorothiazide) reduced the risk for all outcomes more than placebo, and were similar in effectiveness to or more effective than other antihypertensive agents for all outcomes (Table).

## CONCLUSION

In patients with hypertension, low-dose diuretics are as effective as or more effective than other antihypertensive agents as first-line therapy in preventing major cardiovascular disease endpoints.

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### Relative risks (RRs) (95% CIs) for low-dose diuretics (LDDs) vs placebo and other antihypertensive agents at mean 3 to 4 years\*

Outcomes	LDDs vs placebo	LDDs vs $\beta$ -blockers	LDDs vs ACE inhibitors	LDDs vs CCBs	LDDs vs ARBs	LDDs vs $\alpha$ -blockers
CHD	0.79 (0.69 to 0.92)†	0.87 (0.74 to 1.03)	1.00 (0.88 to 1.14)	0.89 (0.76 to 1.01)	0.83 (0.59 to 1.16)	0.99 (0.75 to 1.31)
CHF	0.51 (0.42 to 0.62)†	0.83 (0.68 to 1.01)	0.88 (0.80 to 0.96)†	0.74 (0.67 to 0.81)†	0.88 (0.66 to 1.16)	0.51 (0.43 to 0.60)†
Stroke	0.71 (0.63 to 0.81)†	0.90 (0.76 to 1.06)	0.86 (0.77 to 0.97)†	1.02 (0.91 to 1.14)	1.20 (0.93 to 1.55)	0.85 (0.66 to 1.10)
CVD events	0.76 (0.69 to 0.83)†	0.89 (0.80 to 0.98)†	0.94 (0.89 to 1.00)	0.94 (0.89 to 1.00)	1.00 (0.85 to 1.18)	0.84 (0.75 to 0.93)†
CVD mortality	0.81 (0.73 to 0.92)†	0.93 (0.81 to 1.07)	0.93 (0.85 to 1.02)	0.95 (0.87 to 1.04)	1.07 (0.85 to 1.36)	1.00 (0.75 to 1.34)
Total mortality	0.90 (0.84 to 0.96)†	0.99 (0.91 to 1.07)	1.00 (0.95 to 1.05)	1.03 (0.98 to 1.08)	1.09 (0.96 to 1.22)	0.98 (0.88 to 1.10)

\*ACE = angiotensin-converting enzyme; CCBs = calcium-channel blockers; ARBs = angiotensin-receptor blockers; CHD = coronary heart disease; CHF = congestive heart failure; CVD = cardiovascular disease. CI defined in Glossary. All significant differences favor LDDs. RRs < 1.0 favor LDDs; RRs > 1.0 favor the alternative therapy. †Statistically significant.

## COMMENTARY

Based on major trials and the Joint National Committee recommendations (1, 2), diuretics should be the initial treatment for most hypertensive persons. One shortcoming of some of the recent trials is a lack of direct comparisons between  $\beta$ -blockers and either ACE inhibitors or diuretics.

Psaty and colleagues attempt to add to this literature by using a methodologically complex method, the “network” meta-analysis. The advantage of this technique over a traditional meta-analysis is to combine “direct” comparisons with “indirect” comparisons of drugs (i.e., when they are used in 2 different studies with a common comparison agent). This technique is usually frowned upon because of differences in populations and other sources of variability between studies, but this design is said to minimize those issues. Determining the validity of such a technique is difficult, but comparing the findings with other, more direct results would better support its conclusions; regardless, the analytic method remains a second choice to well-designed clinical trials.

Despite the fact that the authors provided several alternative analytic designs, the results were consistent with most other direct studies show-

ing that diuretics were unsurpassed in decreasing cardiovascular risk outcomes compared with other treatments. In fact, in 6 of the 30 comparisons seen in the Table, diuretics were superior to other treatments. This result led the authors to call for the use of diuretics as the “treatment of first choice” for patients with uncomplicated hypertension.

Unfortunately, most hypertensive patients require > 1 drug for control, and because of a lack of consistency in many trials, we have little information about which combination of drugs is most effective. This is an important next step in determining the most appropriate algorithm for the management of hypertension. What is clear at this time is that most, if not all, patients with uncomplicated hypertension should be started on diuretics as initial therapy.

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## References

1. *JAMA*. 2002;288:2981-97.
2. Chobanian AV, Bakris GL, Black HR, et al. *JAMA*. 2003;289:2560-72.