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What is the best regimen for newly diagnosed hypertension?

EVIDENCE-BASED ANSWER

Low-dose thiazide diuretics (eg, hydrochlorothiazide 12.5 to 25 mg/d) are the best first-line pharmacotherapy for treating uncomplicated hypertension (strength of recommendation [SOR]: **A**, based on randomized trials [RCTs] and 1 meta-analysis). Alternate first-line agents include angiotensin-converting enzyme (ACE) inhibitors, beta blockers, and calcium channel blockers (SOR: **A**, based on RCTs).

EVIDENCE SUMMARY

Three landmark placebo-controlled studies have established that thiazide diuretic–based treatment reduces morbidity and mortality among patients with hypertension.[1–3] Based on these data, thiazide diuretic therapy is considered the gold-standard treatment for uncomplicated hypertension.

Several other clinical trials have subsequently compared the effect of thiazide diuretics with that of other antihypertensive agents (beta-blockers, calcium channel blockers, and alpha-blockers) on patient-oriented outcomes. These were analyzed in a recent meta-analysis of 42 clinical trials that included 192,478 patients randomized to 7 treatment strategies including placebo.[4] Results from the largest antihypertensive clinical trial, the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT), were included in this meta-analysis.[5] Comparative results are depicted in the **Table**. Although these data showed no differences between drug therapies in total and cardiovascular disease mortality, low-dose diuretics reduced certain cardio-vascular endpoints (ie, heart failure, stroke, cardiovascular disease events) more than other drug therapies.

Angiotensin receptor blockers (ARBs) have not been compared with thiazide diuretics in a trial. Two long-term trials have compared an ARB to other types of drug therapy: losartan vs atenolol in the Losartan Intervention for Endpoint Reduction (LIFE) trial,[6] and valsartan vs amlodipine in the Valsartan Antihypertensive Long-term Use Evaluation (VALUE) trial.[7] In the LIFE trial, the primary composite endpoint of cardiovascular death, myocardial infarction, and stroke was less with losartan than atenolol (23.8 vs 27.9 events per 1000 patient-years, losartan and atenolol, respectively; number needed to treat=243 people-years, P=.021).[6] However, in the VALUE trial, the primary endpoint of time to cardiac event was not different between valsartan and amlodipine (25.5 vs 24.7 events per 1000 patient-years, valsartan and amlodipine, respectively; P=.49).[7]

RECOMMENDATIONS FROM OTHERS

The Seventh Report of the Joint National Committee (JNC7) recommended thiazide diuretics as preferred initial agents in uncomplicated hypertension.[8] The European Society of Hypertension/European Society Cardiology recommended either a diuretic, beta-blocker, calcium channel blocker, ACE inhibitor, or ARB for initial therapy stating that blood pressure control to recommended values via any agent is more important than the type of agent used.[9] Both guidelines identified other antihypertensives that may be used in addition to or in place of thiazide diuretics for compelling indications, such as heart failure, diabetes, high-risk cardiovascular disease, chronic kidney disease, post-myocardial infarction, and secondary stroke prevention.

CONTINUED

TABLE

First-line treatments for hypertension

Low-dose diuretic vs	Relative risk (95% CI) of outcome					
	CHD	CHF	Stroke	CVD events	CVD mortality	Total mortality
Beta-blocker	0.87 (0.74–1.03)	0.83 (0.68–1.01)	0.90 (0.76–1.06)	0.89* (0.80–0.98)	0.93 (0.81–1.07)	0.99 (0.91–1.07)
ACE inhibitor	1.00 (0.88–1.14)	0.88* (0.80–0.96)	0.86* (0.77–0.97)	0.94 (0.89–1.00)	0.93 (0.85–1.02)	1.00 (0.95–1.05)
Calcium channel blocker	0.89 (0.76–1.01)	0.74* (0.67–0.81)	1.02 (0.91–1.14)	0.94 (0.89–1.00)	0.95 (0.87–1.04)	1.03 (0.98–1.08)
Alpha-blocker	0.99 (0.75–1.31)	0.51* (0.43–0.60)	0.85 (0.66–1.10)	0.84* (0.75–0.93)	1.00 (0.75–1.34)	0.98 (0.88–1.10)

*Denotes statistically significant difference favoring low-dose diuretics ($P<.05$).
CI, confidence interval; CHD, congestive heart disease; CVD, cardiovascular disease; ACE, angiotensin-converting enzyme.
Source: Psaty BM, Lumley T, Furberg CD, et al, *JAMA* 2003.[4]

CLINICAL COMMENTARY

Thiazide diuretics: first or second agent for patients with hypertension

Skeptics argue that other antihypertensives are equal to thiazides. However, thiazides are the least expensive agents (1-year hydrochlorothiazide 25 mg/d is <$25.00). This aspect of therapy supports thiazides as first-line pharmacotherapy. The debate of which agent to use first may be moot considering most hypertensive patients require 2 or more drugs to achieve a systolic blood pressure goal of <140 mm Hg. In addition, the JNC7 recommended starting with 2 agents for patients far from their blood pressure goal (eg, systolic blood pressure ≥160 mm Hg). Therefore, even if a thiazide is not the initial agent (because of preference or other compelling indications) it should be the second agent for most patients.

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