

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. 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. Results from the largest antihypertensive clinical trial, the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALL-HAT), were included in this meta-analysis.

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, and valsartan vs amlodipine in the Valsartan Antihypertensive Long-term Use Evaluation (VALUE) trial. 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, \( P=\cdot021 \)). 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; \( P=\cdot49 \)).

■ RECOMMENDATIONS FROM OTHERS
The Seventh Report of the Joint National Committee (JNC7) recommended thiazide diuretics as preferred initial agents in uncomplicated hypertension. 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. 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.
**TABLE**

First-line treatments for hypertension

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

*Denotes statistically significant difference favoring low-dose diuretics (*P* < .05).

CI, confidence interval; CHD, congestive heart disease; CVD, cardiovascular disease; ACE, angiotensin-converting enzyme.


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**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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**REFERENCES**


