

**Which antihypertensives are more effective in reducing diastolic hypertension versus systolic hypertension?  
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The most important reason for treating hypertension in primary care is to prevent adverse health outcomes and reduce the risk for premature death.<sup>1</sup> Hypertension is defined as elevated blood pressure: systolic blood pressure (SBP)  $\geq 140$  mmHg or diastolic blood pressure (DBP)  $\geq 90$  mmHg. Isolated diastolic hypertension is a condition in which only the DBP remains elevated while the SBP remains normal.<sup>2</sup> This condition is more commonly observed in younger patients (aged  $< 50$  years) compared to older patients (aged  $\geq 60$  years), since increases in DBP tend to lessen with increasing age.<sup>3</sup>

Treatment options solely focused on reducing DBP have received little attention in the medical literature. Most of the current hypertension clinical guidelines make treatment recommendations with a greater emphasis on treating hypertension based on SBP.<sup>1,3-5</sup> Such an approach is in line with the premise that SBP is perhaps the more important factor in determining the risk for adverse health outcomes.<sup>2</sup> The following will review treatment guidelines and the medical literature in order to determine which antihypertensives are more effective in reducing DBP compared to SBP.

The eighth report of the Joint National Committee (JNC8) for Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (2014) in adults recommends initiating treatment based on SBP/DBP, age, race, and presence of diabetes or chronic kidney disease (CKD).<sup>1</sup> For patients aged  $\geq 60$  years, treatment should be initiated if SBP  $\geq 150$  mmHg and/or DBP  $\geq 90$  mmHg. For patients aged  $< 60$  years, treatment should be initiated if SBP  $\geq 140$  mmHg and/or DBP  $\geq 90$  mmHg. Unless the patient is black or presents with comorbid conditions such as diabetes or CKD, the JNC8 recommends starting therapy with 1 of the following classes of agents: angiotensin-converting enzyme inhibitors (ACEIs), angiotensin receptor blockers (ARBs), calcium channel blockers (CCBs), or diuretics. For black patients, the JNC8 recommends starting therapy with either a thiazide type diuretic or CCB. The guideline does not specify which agents are more effective for lowering DBP.

Similar to the recommendations of the JNC8, the American Society of Hypertension (ASH) and the International Society of Hypertension (ISH) also recommend specific antihypertensive classes based on age, race, and the presence of comorbidities.<sup>3</sup> The ASH/ISH guideline also provides general information for each class of agents but lacks specific recommendations for lowering DBP.

The American Heart Association (AHA), American College of Cardiology (ACC), and the Centers for Disease Control and Prevention (CDC) also recommend treating hypertension based on the initial SBP or DBP.<sup>4</sup> Treatment selection is the same regardless of diastolic or systolic elevation. In patients presenting with SBP  $\geq 140$  mmHg or DBP  $\geq 90$  mmHg, lifestyle modification is recommended, followed by initiation of a thiazide type diuretic. In patients presenting with SBP  $\geq 160$  mmHg or DBP  $\geq 100$  mmHg, monotherapy with an ACEI or CCB may be initiated or dual therapy involving a combination of a thiazide type diuretic and an ACEI, ARB, or CCB. No specific recommendations are made based solely on DBP elevation.

The European Society of Hypertension (ESH) and the European Society of Cardiology (ESC) recommend targeting a DBP goal of <90 mmHg in the general population.<sup>5</sup> A lower goal of <85 mmHg is recommended for patients with diabetes. However, the ESH/ESC guideline does not specify which drug class is preferred for treating elevated DBP. Recommendations for specific classes of antihypertensives are based on age, gender, and comorbid conditions. The ESH/ESC broadly recommends the use of a diuretic, beta-blocker, CCB, ACEI, or ARB for initial treatment of hypertension.

In addition to the guidelines, a literature search was conducted to identify head-to-head trials comparing the effectiveness of different classes of antihypertensives for lowering DBP. There appears to be a lack of high-quality research demonstrating the DBP-lowering effects of commonly used antihypertensive agents. Because the main goal of treating hypertension is to prevent chronic medical conditions (e.g., cardiovascular events) and premature death, most large-scale trials have focused on measuring the effectiveness of antihypertensive classes in reducing the risk for these events rather than the numerical reduction of blood pressure. The efficacy of individual antihypertensive drug classes in treating primary hypertension was reviewed by the Cochrane Collaboration on several occasions.<sup>6-10</sup> The reviews were focused on the blood pressure lowering effects of ACEIs, ARBs, beta-blockers, and loop/thiazide type diuretics. The Cochrane review of CCBs is currently unavailable. Brief summaries of each review are in Appendix 1. Comparing the DBP-lowering effectiveness between the different agents should be done with caution as strong conclusions may only be drawn from well-designed, comparative trials.

In summary, current guidelines recommend managing hypertension with lifestyle modification and medication if DBP is  $\geq 90$  mmHg, regardless of SBP. In terms of selecting an antihypertensive medication for treatment, current guidelines make preferences for specific agents based on age, race, and the presence of comorbid conditions, rather than the type of hypertension (i.e., diastolic hypertension). With the current available literature, it is difficult to determine which antihypertensive agent is most effective in reducing DBP.

#### References:

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**Table 1: Efficacy of antihypertensives in lowering DBP (Cochrane review summary).**

Drug Class	Best Estimate of DBP-Lowering Effect	Notes
ACEI <sup>6</sup> (2009)	<p>Compared to placebo, ACEI reduced DBP by an average of 5 mmHg</p> <ul style="list-style-type: none"> <li>92 trials were reviewed, including 14 different ACEIs (N=12,954)</li> </ul>	<p>Individual drugs were also reviewed: (change in DBP in mmHg, 95% CI)*</p> <ul style="list-style-type: none"> <li>- Captopril 50 mg/day: -5.43, -6.47 to -4.40</li> <li>- Enalapril 20 mg/day: -4.80, -5.81 to -3.79</li> <li>- Fosinopril 20 mg/day: -5.00, -6.94 to -3.05</li> <li>- Lisinopril 10-80 mg/day: -4.76, -5.92 to -3.60</li> <li>- Quinapril 20 mg/day: -3.35, -5.98 to -0.72</li> <li>- Ramipril 5-10 mg/day: -4.14, -5.81 to -2.48</li> </ul>
ARB <sup>7</sup> (2009)	<p>Compared to placebo, ARB reduced DBP by an average of 5 mmHg</p> <ul style="list-style-type: none"> <li>46 RCTs were reviewed, including 9 different ARBs (N=13,451)</li> </ul>	<p>Individual drugs were also reviewed: (change in DBP in mmHg, 95% CI)**</p> <ul style="list-style-type: none"> <li>- Losartan 50-150 mg/day: -3.59, -4.17 to -3.00</li> <li>- Irbesartan 75-300 mg/day: -5.09, -5.82 to -4.36</li> <li>- Valsartan 80-320 mg/day: -4.34, -4.96 to -3.72</li> </ul>
Beta-blockers <sup>8</sup> (2010)	<p>DBP reduction in mmHg (95% CI)</p> <ul style="list-style-type: none"> <li>At recommended starting dose: <ul style="list-style-type: none"> <li>-4.25 (-5.11 to -3.39) <ul style="list-style-type: none"> <li>13 studies were included in the analysis (N=669)</li> </ul> </li> </ul> </li> <li>At 2-times recommended starting dose: <ul style="list-style-type: none"> <li>-6.25 (-7.17 to -5.34) <ul style="list-style-type: none"> <li>8 studies were included in the analysis (N=591)</li> </ul> </li> </ul> </li> </ul>	<p>The review was focused on measuring DBP-lowering effect when beta-blockers were added as a second-line agent to an existing therapy</p>
Loop diuretic <sup>9</sup> (2015)	<p>At various doses, loop diuretics reduced DBP by an average of 4.4 mmHg (95% CI: -5.9 to -2.8)</p> <ul style="list-style-type: none"> <li>9 trials were reviewed, including 5 different loop diuretics (N=460)</li> </ul>	<ul style="list-style-type: none"> <li>- This estimate was rated as a low quality and future studies are likely to have important impact on the estimate of DBP lowering effects</li> <li>- The reviewers claimed that the DBP-lowering effect of loop diuretics is not significantly different from thiazides, ACEI, ARB, or renin inhibitors</li> </ul>



Drug Class	Best Estimate of DBP-Lowering Effect	Notes
Thiazides <sup>10</sup> (2014)	DBP reducing effects of hydrochlorothiazide at various doses are listed below (in mmHg, 95% CI): <ul style="list-style-type: none"> <li>• 3-6.25 mg/day: -2.4 (-3.7 to -1.2)</li> <li>• 12.5 mg/day: -3.1 (-3.7 to -2.5)</li> <li>• 25 mg/day: -3.3 (-3.8 to -2.8)</li> <li>• 50-100 mg/day: -4.7 (-6.1 to -3.3)                             <ul style="list-style-type: none"> <li>○ 33 trials were included in this analysis (N=7,284)</li> </ul> </li> </ul>	- Please note that the reduction estimates for doses of 12.5 and 25 mg/day were rated as high quality and future studies are unlikely to change the estimate - The authors state that thiazides as a class have a greater effect on reducing SBP than DBP

ACEI=angiotensin-converting enzyme inhibitor; ARB=angiotensin receptor blocker; CI=confidence interval; DBP=diastolic blood pressure; SBP=systolic blood pressure

\* The 6 ACEIs that were mentioned as examples of ACEIs in the review summary were selected; noted excluded agents not available in the U.S.

\*\* Top 3 ARBs with the most number of qualified studies were selected