

antihypertensive classes in preventing strokes and had a less favorable side effect profile; therefore, they should be reserved for adults with compelling indications.⁷

Recommendation-Specific Supportive Text

1. The primary goal of treatment should be to reduce BP to the target level, considering the underlying CVD risk and compelling indications. High-quality RCTs have demonstrated that 4 drug classes, thiazide-type diuretics, long-acting dihydropyridine CCB, ACEi and ARB, prevent CVD compared with placebo.¹⁻⁵ In head-to-head comparisons of first-line therapy, different drug classes show varying capacities to prevent specific CVD events.^{6,7} While there are subtle differences among thiazide-type diuretics, long-acting dihydropyridine CCB, and ACEi and ARB, the general pattern indicates a similar effect in preventing CVD. Likewise, the observed CVD prevention with these agents is similar to that expected on the basis of BP lowering.⁸ In a large pragmatic RCT comparing HCTZ 25 mg to chlorthalidone 12.5 mg, switching from HCTZ to chlorthalidone did not lower the rates of MACE.⁹ The subgroup of patients with ASCVD had greater benefit with chlorthalidone than HCTZ; however, the design of the study made it difficult to exclude the possibility that choice of a longer-acting diuretic such as chlorthalidone is preferable to use of a shorter-acting agent such as HCTZ.

5.2.4. Choice of Initial Monotherapy Versus Initial Combination Drug Therapy

Recommendations for Choice of Initial Monotherapy Versus Initial Combination Drug Therapy
Referenced studies that support the recommendations are summarized in the [Evidence Table](#).

COR	LOE	RECOMMENDATIONS
1	B-R	1. In adults with stage 2 hypertension (SBP $\geq$ 140 mm Hg and DBP $\geq$ 90 mm Hg), initiation of antihypertensive drug therapy with 2 first-line agents of different classes, ideally in a single-pill combination (SPC), is recommended to improve BP control and adherence. ¹⁻⁶

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COR	LOE	RECOMMENDATIONS
2a	C-EO	2. In adults with stage 1 hypertension (SBP 130-139 mm Hg and DBP 80-89 mm Hg), initiation of antihypertensive drug therapy with a single first-line antihypertensive drug is reasonable, with dosage titration and sequential addition of other agents as needed to achieve BP control.
3: Harm	A	3. In adults with hypertension, simultaneous use of an ACEi, ARB, and/or renin inhibitor in combination is not recommended due to the potential for harm. ⁷⁻⁹

Synopsis

Pharmacological agents are an integral tool in the treatment of hypertension. As BP is regulated by several complementary biological systems, most patients require $\geq$ 2 antihypertensive medications to achieve BP control. Historically, a stepped-care approach was recommended, starting with monotherapy then titrating the dose or adding a second agent as needed. No RCTs have compared initial stepped care with initial combination therapy. Combining antihypertensive medications with complementary mechanisms enhances BP-lowering effects and may reduce side effects.² For example, combining an RAS blocker with a thiazide-type diuretic reduces the likelihood of hypokalemia or hyperkalemia, and combining an ACEi or ARB with a dihydropyridine CCB reduces the incidence and severity of lower leg swelling. Combination therapy is more effective, efficient, and consistent in lowering BP and improves adherence when using an SPC compared with stepped-care therapy.¹⁰ However, a stepped-care approach can be effective for BP lowering if well-executed.¹¹ Exceptions include stage 1 hypertension, where some patients can achieve and maintain BP control with a single agent, especially those with initial BP close to target. Initial combination therapy is recommended for stage 2 hypertension and some high-risk patients with stage 1 hypertension (eg, non-Hispanic Black adults, ASCVD risk $>$ 7.5%) using 2 agents from different classes, preferably in an SPC to improve adherence and BP control (Section 5.2.5, “Antihypertensive Medication Adherence Strategies”).¹⁻³ Few RCTs have compared different combinations head-to-