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Q / Which combination drug therapies are most effective for hypertension?

EVIDENCE-BASED ANSWER

A / INSUFFICIENT EVIDENCE exists to determine which specific combinations most effectively decrease cardiovascular morbidity and mortality, although combinations of hypertension medications at lower doses generally reduce cardiovascular outcomes (stroke, coronary heart disease) more than monotherapy (strength of recommendation [SOR]: A, large meta-analyses).

The combination of benazepril and amlodipine reduces the composite endpoint of cardiovascular events and deaths more than benazepril plus hydrochloro-

thiazide with similar rates of adverse effects (SOR: A, randomized controlled trial [RCT]).

Combining an angiotensin converting enzyme inhibitor (ACE-I) with a thiazide, β -blocker, or calcium channel blocker produces side effects similar to monotherapy, as does combining an angiotensin receptor blocker (ARB) with a thiazide or calcium channel blocker (SOR: A, meta-analyses). However, an ACE-I combined with an ARB increases the risk of renal complications and death more than monotherapy (SOR: A, RCT).

Evidence summary

A meta-analysis of 147 RCTs with a total of 464,000 patients demonstrated better cardiovascular outcomes for combination therapy vs monotherapy among patients 60 to 69 years of age with diastolic blood pressures 90 mm Hg or higher. Investigators randomized participants with no history of vascular disease, a history of coronary heart disease, or a history of stroke to monotherapy or a combination of 3 drugs from any class at half-standard doses. Combination therapy reduced both coronary heart disease and stroke (number needed to treat [NNT] to prevent 1 new case of coronary heart disease=4, NNT to prevent 1 stroke=3).¹

Another meta-analysis of 61 prospective observational studies with a total of 1 million patients showed that for every coronary event or stroke prevented by dou-

bling the dose of a single drug, 4 events were prevented by using combination therapy.² A 3-point reduction in systolic blood pressure resulted in a 5% to 10% reduction in heart disease and stroke.¹

A meta-analysis of 42 trials with a total of almost 11,000 patients found that combining any 2 drug classes at low doses decreased diastolic blood pressure more than doubling the dose of a single drug (9 mm Hg vs 6 mm Hg).³

ACE-I plus β -blocker or calcium channel blocker outperforms thiazide combos

The combination of an ACE-I plus a β -blocker lowered systolic blood pressure more than ACE-I monotherapy (22.9 mm Hg vs 12.5 mm Hg) in an RCT with 48 patients.⁴ More patients taking an ACE-I plus a calcium channel blocker achieved the primary endpoint (reductions in systolic blood pressure

TABLE

Efficacy and safety of drug combinations for essential hypertension*

	Combined with				
	ACE-I	ARB	β -blocker	Calcium channel blocker	Thiazide
ACE-I efficacy	N/A	16-27 mm Hg systolic BP drop (based on RCT, N=25,260) ¹⁰	22.9 mm Hg systolic BP drop (based on RCT, N=48) ⁴	13.7-20.9 mm Hg systolic BP drop [†] (based on RCT, N= >10,000) ⁵	12.9 mm Hg systolic BP drop (based on RCT, N=11,506) ^{6,7}
ACE-I safety	N/A	Increased risk of death, dialysis, doubled creatinine (NNH=100 for combined endpoint) ¹⁰	Side effects similar to ACE-I monotherapy ⁴	Side effects similar to ACE-I monotherapy ^{5,6}	Side effects similar to ACE-I monotherapy ^{6,7}
ARB efficacy	16-27 mm Hg systolic BP drop (based on RCT, N=25,260) ¹⁰	N/A	Unknown	12-20 mm Hg systolic BP drop (based on RCT, N=926) ⁹	14-25 mm Hg systolic BP drop (based on subgroup analysis of large RCT and RCT, N=261) ⁸
ARB safety	Increased risk of death, dialysis, doubled creatinine (NNH=100 for combined endpoint) ¹⁰	N/A	Unknown	Side effects similar to ARB monotherapy ⁹	Combination increased dizziness more than ARB monotherapy (NNH=33) ⁸

ACE-I, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; BP, blood pressure; N/A, not applicable; NNH, number needed to harm; RCT, randomized controlled trial.

*The efficacy and safety of pairing the drugs in the column at left with those in the row at top. All combinations used approximately half the maximum dose of each component.

[†]Significant decrease in cardiovascular mortality.

≥ 25 mm Hg) than did patients randomized to monotherapy (74.2% vs 53.9%; NNT=5).⁵

In an RCT of 11,506 patients, benazepril plus amlodipine decreased blood pressure more than benazepril plus hydrochlorothiazide (difference=0.9 mm Hg systolic, 1.1 mm Hg diastolic) and improved the composite outcome of cardiovascular events and deaths (absolute risk reduction=2.2%; NNT=45).⁶ Rates of adverse drug reactions were similar among patients taking ACE-I monotherapy and combinations of benazepril plus amlodipine or benazepril plus hydrochlorothiazide.^{4,6}

ARB plus a thiazide lowers BP more than monotherapy

Five short-term RCTs comparing ARB-

thiazide combinations with monotherapy measured changes in blood pressure rather than morbidity and mortality. In these studies, sponsored by pharmaceutical companies, combination treatment more often produced blood pressures within the goals of the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC-VII) than monotherapy (62% vs 37%; NNT to reach goal=4 [approximately]).⁷⁻⁸ An ARB plus hydrochlorothiazide lowered blood pressure more effectively than either drug alone but produced more dizziness (8.5% vs 4.7%; $P=.002$).⁷

In an RCT of 926 patients who had failed monotherapy with an ARB, 74.8% treated

with an ARB plus a calcium channel blocker achieved blood pressures <140/90.⁹ Adding a calcium channel blocker decreased blood pressures by about 19 mm Hg systolic and 11 mm Hg diastolic with few adverse drug reactions.

How safe is combination therapy?

Participants in a 6-year RCT of 25,260 patients had more adverse outcomes with an ARB plus ACE-I combination than monotherapy (number needed to harm=100 to cause composite endpoint of death, dialysis, or creatinine doubling).¹⁰ For most other combinations, the safety profile is unknown or similar to monotherapy.

The TABLE summarizes the efficacy and

safety profiles of antihypertensive drug combinations.⁴⁻¹⁰

Recommendations

Both the 2003 JNC-VII and the 2008 Canadian Hypertension Education Program recommendations for managing hypertension advise lowering blood pressure to <140/90 mm Hg in all patients and <130/80 mm Hg in patients with diabetes and chronic kidney disease.^{11,12} Both guidelines also suggest starting therapy with 2 drugs when blood pressure is more than 20 mm Hg above systolic goal or 10 mm Hg above diastolic goal, but they do not endorse specific combinations.

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Combining an angiotensin converting enzyme inhibitor with an angiotensin receptor blocker increases the risk of renal complications and death more than monotherapy.

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