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

**EVIDENCE-BASED ANSWER**

**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 hydrochlorothiazide 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 doubling 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 end point (reductions in systolic blood pressure.
≥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
Combining an angiotensin converting enzyme inhibitor with an angiotensin receptor blocker increases the risk of renal complications and death more than monotherapy.

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). 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.

References