

PRIORITY UPDATES FROM THE RESEARCH LITERATURE (PURLS)

Are Single-Pill Antihypertensive Combinations Superior to Multi-Pill Regimens at Reducing All-Cause Mortality and Cardiovascular Events?

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Single-pill antihypertensive combinations are superior to multi-pill antihypertensive regimens at reducing all-cause mortality and cardiovascular events and they result in longer medication persistence (length of time taking medication). (J Am Board Fam Med 2025;38:1117–1119.)

Keywords: Antihypertensive Drugs, Drug Combinations, Medication Regimen

Strength of Recommendation

B: Based on a single, moderate quality, retrospective, propensity-matched cohort study using claims data.¹

Illustrative Case

A 56-year-old female with a history of hypertension, diabetes, hypothyroidism, hyperlipidemia and prior Cerebrovascular Accident (CVA) presents to your office for follow up on her hypertension. She currently takes valsartan 80 mg and amlodipine 10 mg and reports near daily compliance. Blood pressure in the office is 148/86 mmHg. Should you recommend a switch to a single-pill antihypertensive?

Clinical Context

Primary care clinicians are aware that many patients will require multiple medications to achieve blood pressure control. Patients are often hesitant about adding additional medicines. Increasing the complexity of their

treatment can lead to poor compliance with medications. However, decreasing the number of pills needed daily can improve compliance. Our current practice of prescribing combinations of multiple classes of pills as individual pills (MPC) versus prescribing one single-pill combination (SPC) no longer seems to be the best practice.

Systolic high blood pressure is the most prevalent and important modifiable cardiovascular risk factor.¹ The 2017 American College of Cardiology (ACC)/American Heart Association (AHA) guidelines recommend that all stage 1 hypertension patients with an estimated 10-year atherosclerotic cardiovascular disease (ASCVD) risk of 10% and all patients with stage 2 hypertension ($\geq 140/\geq 90$ mmHg) should be started on pharmacotherapy as well as Lifestyle Management (LSM).² Pharmacotherapy should be initiated with dual, single-pill combinations or with combination pills.³

Despite hypertension being a leading risk factor for cardiovascular disease, studies illustrate that 40 to 74% of people are nonadherent to their antihypertensive medications.⁴ Various interventions have tried to improve adherence to medication therapy including: self or home monitoring of blood pressure, education directed at patients or health care professionals, telephone reminders, and increasing frequency of follow-up appointments. Most of these interventions illustrated mixed evidence for improvement that was unlikely to be associated with large net reductions in blood pressure.^{5–7} However, simplifying dosing regimens, especially by reducing the number of daily doses, has been shown to improve compliance with medication.⁸

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One strategy to reduce the number of daily medication doses is to combine pills, such as with SPC.

Methods

This article was identified as a potential PURL through the standard systematic methodology.¹⁴ An additional literature search was conducted using PubMed with the terms: Antihypertensive agents, hypertension regimen combination pills, medication adherence hypertension treatment, fixed dose combination medications.

Study Summary

This is a subanalysis of a retrospective claims data analysis assessing all-cause mortality, incidence of cardiovascular events and persistence to medication in patients treated with a combination of renin-angiotensin blockers. For each of the 4 drug combinations, patients with SPCs ($n = 28,999$) were matched with patients with MPCs ($n = 28,999$) in a 1:1 fashion to compare the use of a SPC with equidose MPC. The primary outcome was all-cause mortality. Secondary outcomes included acute hospitalizations (regardless of cause), stroke, myocardial infarction, transient ischemic attack, coronary heart disease, heart failure, a composite end point of all-cause hospitalizations and all-cause death, and medication persistence (defined as the length of time a medication is taken after it is started).

Results showed a lower mortality rate in all 4 of the SPCs compared with the MPCs with Incident Risk Ratios [IRR] ranging from 0.51–0.53. The composite outcome of all-cause hospitalization and all-cause death was also lower in all 4 SPC as compared with the MPC groups. The incidence of cardiovascular events was significantly lower in the SPC groups compared with MPC groups in 15 of the 20 subcategories analyzed, including coronary artery disease and heart failure events. Secondary outcomes also favored the SPC groups with lower hospital readmissions in all 4 drug combination groups.

Medication persistence was significantly higher after one year in the SPC groups compared with MPC groups.

What Is New

This study demonstrated decreased all-cause mortality and cardiovascular event rates in patients treated with a single combination pill of antihypertensive

medication compared with patients treated with equal-dose multiple individual pills. Other studies have demonstrated that SPCs lead to greater blood pressure reduction and better medication adherence than multiple pill combinations (MPCs), but this study demonstrates a connection between SPCs and decreased cardiovascular outcomes.

Only about 1 in 4 new patients who qualify for more than one antihypertensive agent are started on a fixed dose combination.⁹ This study lends further impetus to adjusting our practice habits and moving toward prescribing SPCs for the treatment of hypertension, especially when the patient needs more than one agent initially.

Caveats

This study did not provide information about the included German patient population, including demographics or comorbidities, making assumptions about generalization challenging. The propensity score of 0.001 in this study indicates excellent matching in the covariates of the two groups.¹⁰ Additional statistical analysis was performed by evaluating independent health events (hip replacement and knee replacement) between the groups. No significant differences were found which supports the conclusion that the internal validity of the study was strong.

Challenges to Implementation

The biggest challenge to implementation will be changing ingrained prescribing habits, especially the habit of starting with one class of medicine and adding on with additional pills rather than converting to fixed dose combinations. Some physicians may be concerned about increased side effects with combination medicines. Meta analysis has shown minimal difference in side effect profiles when using combination type pills.¹¹ Cost might be a concern, but it has been shown that patients taking SPC have approximately \$1,000 lower cost annually than patients taking equivalent doses with multiple pills.¹² The availability of SPC with the exact components a physician desires is limited to currently existing preparations. There are currently medications representative of most class combinations, but exact dose combinations may be less available. This may change with the advent of pharmaceutical 3-day printing technology.¹³

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