Expanding Role for Combination Drug Therapy in the Initial Treatment of Hypertension?

Theodore A. Kotchen

Both the seventh report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure and the European Society of Hypertension have recommended initiating antihypertensive therapy with a single agent in patients with stage 1 or grade 1 hypertension (systolic <160 mm Hg and diastolic <100 mm Hg).\(^1,^2\) Although the seventh report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure recommends initiating drug therapy with a thiazide-type diuretic for “most patients,” the report acknowledges that selection of an initial single agent may be influenced by patient demographics, comorbidities, and physiological profiling (eg, hemodynamic values and renin-sodium profiling). Initiating drug therapy with >1 agent is recommended for patients with blood pressure >20/10 mm Hg above goal\(^3\) or for patients with grade 2 or grade 3 hypertension (systolic ≥160 mm Hg and/or diastolic ≥100 mm Hg) or high overall cardiovascular risk where early blood pressure control may be desirable.\(^2\)

However, based in part on data from the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial, ≈75% of patients with hypertension will require therapy with >1 antihypertensive agent to achieve recommended blood pressure goals. Based on analyses of large numbers of published clinical trials, overall, it has been estimated that the blood pressure–lowering capacities of low doses of 2 agents used in combination are additive\(^4\) or that the average percentage effects of the second medication are 84% and 65% for systolic and diastolic blood pressures, respectively. Consequently, initiating therapy with >1 agent may be more efficient and efficacious than sequential monotherapy. A potential additional advantage of combination therapy is the reduction of drug adverse effects by allowing lower doses of the agents used in combination. In a meta-analysis of a large number of trials, Wald et al\(^5\) reported that the extra blood pressure reduction from combining drugs is ≈5 times greater than doubling the dose of 1 drug.

In a recent position paper dealing with combination therapy, the American Society of Hypertension recommended the following: (1) routinely use combination therapy to achieve blood pressure targets; (2) routinely initiate combination therapy in patients who require >20/10 mm Hg of blood pressure reduction to achieve target blood pressure; and (3) initiate combination therapy in stage 1 patients (at the physician’s discretion), especially when the second agent will improve the adverse effect profile of initial therapy.\(^3\) Both the American Society of Hypertension report and the European Society of Hypertension have recommended specific drug combinations based on combining agents that either interfere with different pressor mechanisms or that block counterregulatory responses.

In this issue of Hypertension, Corrao et al\(^6\) compare the effects of initiating antihypertensive therapy in daily clinical practice with a single agent or with a combination of drugs on cardiovascular events. Data were retrieved from the health services databases of Lombardy, a region of Italy with a population of 9 million. This population is covered by the National Health Service, and Lombardy residents between ages 40 to 79 years were the target population. Individuals who were first prescribed antihypertensive drugs during calendar years 2000 and 2001 were identified, and outcome data for this cohort were tracked for ≈7 years. “Cases” were members of the cohort who, during follow-up, experienced ≥1 coronary or cerebrovascular event as diagnosed at hospital discharge (n=10,688). For each case, 3 controls were randomly selected from this cohort, matched for sex, age, and date of index prescription. Eighty-one percent of both cases and controls were initially treated with monotherapy. Cases had a higher prevalence of comorbidities, as assessed by the use of other drugs (digitalis or nitrates, lipid-lowering agents, other cardiovascular drugs, and antidiabetic drugs) and by a Charlson comorbidity index score. Overall, there were significantly fewer cardiovascular outcomes in patients initially treated with combination antihypertensive therapy compared with those initially treated with monotherapy. With initial combination therapy, the incidence of cerebrovascular and coronary events was reduced by 12% and 8%, respectively, compared with patients initially treated with monotherapy. The most striking reduction in cardiovascular events was observed in those patients treated initially with combination therapy and maintained on combination therapy throughout the period of follow-up—a 26% reduction of cardiovascular outcomes compared with patients treated with monotherapy, both initially and throughout the follow-up period.

Because a limited amount of clinical information was available for this cohort, the investigators used a Monte-Carlo sensitivity analysis, based on a separate population, to account for unmeasured confounders. Data were obtained from a Health Search/Cambridge Structural Database, which pro-
provided patient records from >700 physicians. Patients who started monotherapy or combination antihypertensive therapy from 2004 to 2007 were identified (n=41,199) and were classified by severity of hypertension, presence of comorbidities, and body mass index. Compared with patients started on monotherapy, patients on combination therapy had a higher prevalence of severe hypertension, more comorbidities, and a higher body mass index. The statistical significances of differences in cardiovascular outcomes comparing monotherapy with combination therapy observed in the original Lombardy cohort were adjusted for these confounders. For each confounder, after this adjustment, the statistical significance of the cardiovascular protective effects of combination therapy that were observed in the original cohort was amplified.

A primary strength of this study, which involves large numbers of subjects, is the focus on definitive cardiovascular end points. The results seem to make a convincing case for the superiority of combination antihypertensive therapy compared with monotherapy. Possible reasons for this difference are only conjectural. Unfortunately, blood pressure measurements are not available, although, based on earlier clinical trial data, it is likely that combination therapy resulted in more effective control of blood pressure. In addition, no information is provided about possible associations between cardiovascular outcomes and specific agents used for monotherapy and combination therapy, although it appears that this information would be available in the National Health Service database. Perhaps not surprisingly, patients treated with combination therapy had a higher risk profile and more comorbidities than patients treated with monotherapy. Statistical adjustment for some of these potential confounders was based on data obtained in a separate population. The details of this analysis are not provided, and, consequently, the somewhat surprising conclusions are suspect, that is, statistical adjustment for potential confounders amplified rather than attenuated the superiority of combination therapy. Another possible reason for the more favorable effect of combination therapy on cardiovascular end points relates to adherence to the prescribed regimen over time. In a recent publication, based on a separate analysis of a Lombardy cohort that appears to overlap with the same cohort studied in the current publication, Corrao et al. reported that the frequency of drug discontinuation was reduced in patients treated with combination therapy (either fixed-dose combination or 2 separate agents) than in patients treated with monotherapy.

In the final analysis, this is an observational study with limited clinical data and with potentially important confounding differences between those patients treated with monotherapy or with combination therapy. Nevertheless, results of this study might be the impetus for confirmatory, prospective, randomized clinical trials to compare the effects of combination therapy, specific combinations of drugs, and monotherapy on hypertension control over time and on cardiovascular end points.

**Disclosures**

None.

**References**


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