

HYPERTENSION BENEFITS OF COMBINED THERAPY

A fixed-dose combination of two antihypertensive drugs lowers blood pressure by a greater extent than the maximum dose of either drug alone. This finding comes from a phase III trial conducted at 401 sites in the USA.

The drugs used in the double-blind trial were nebivolol (a highly selective β_1 -receptor antagonist and β_3 -receptor agonist that produces nitric oxide) and valsartan (an angiotensin II-receptor blocker). The investigators randomly allocated 4,161 patients with stage 1–2 hypertension to various treatment strategies or placebo. Active treatment comprised a daily fixed dose of nebivolol (5 mg or 20 mg), valsartan (80 mg or 160 mg), or a combination of nebivolol and valsartan (5 mg and 80 mg, 5 mg and 160 mg, or 10 mg and 160 mg, respectively). Patients received the drugs for 4 weeks, and then the doses were doubled during weeks 4–8.

The primary comparison was between the highest doses of combination therapy and each monotherapy. The reduction in diastolic blood pressure compared with baseline was significantly greater with the fixed-dose combination of nebivolol 20 mg and valsartan 320 mg (–15.7 mmHg) than with either nebivolol 40 mg alone (–14.4 mmHg) or valsartan 320 mg alone (–11.2 mmHg). Similarly, the reduction in systolic blood pressure was significantly greater with the highest fixed-dose combination (–17.8 mmHg) than with either the highest dose of nebivolol alone (–15.1 mmHg) or the highest dose of valsartan alone (–14.8 mmHg). Approximately one-third of all patients reported at least one adverse event that was considered to be mild or moderate in severity. A total of 27 serious adverse events occurred, none of which was judged to be treatment-related.

In a Commentary published with the trial report in *The Lancet*, Bernard Waeber and François Feihl note the 1994 FDA criteria for approving a fixed-dose combination of antihypertensive drugs for first-line treatment: “the combination must be superior [in efficacy] to either component administered alone, and this benefit must not be obtained at the expense of tolerability”. According to Waeber and Feihl, “these criteria are clearly met by the nebivolol and valsartan combination”.

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Original article Giles, T. D. et al. Efficacy and safety of nebivolol and valsartan as fixed-dose combination in hypertension: a randomised, multicentre study. *Lancet* **383**, 1889–1898 (2014)