

COMMENTARY

Safety and clinical outcome in combination therapy for high-risk elderly hypertensive patients

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To achieve the optimal target blood pressure level (<140/90 mm Hg) for the prevention of cardiovascular events, various combinations of antihypertensive drugs are often required.¹ Meta-analysis demonstrated that the blood pressure reduction effects of different categories of drugs were additive and adverse symptoms attributable to thiazide diuretics, β -blockers and calcium channel blockers (CCBs) were strongly dose related, whereas angiotensin receptor blockers (ARBs) caused no increase in symptoms.² The extra blood pressure reduction from combining drugs from two different classes is approximately five times greater than doubling the dose of one drug,³ whereas the prevalence of symptoms with two drugs in combination was less than additive and adverse metabolic effects were negligible at half the standard dose, indicating that low-dose combination treatment increases the efficacy of treatment and reduces adverse drug reactions.² According to the current Japanese Society of Hypertension Guideline for the Management of Hypertension (JSH 2014),¹ if antihypertensive effects are insufficient, among the combinations of two drugs, those of angiotensin-converting enzyme (ACE) inhibitor or ARB+CCB, ACE inhibitor or ARB+thiazide diuretic and CCB+thiazide diuretic are recommended. It is reported that, according to the trends in the prescription of antihypertensive drugs in Japan, the two most prescribed classes of antihypertensive drugs were ARBs and CCBs, and the prescription rate for thiazide diuretics has increased, but the rate of its increase was unchanged during the study period.⁴

In this issue, Saruta *et al.*⁵ reported findings regarding safety and tolerability as a sub-analysis of the Combinations of OLMesartan (COLM) study. Few clinical studies have prospectively compared regimens for combination therapy in elderly hypertensive patients. The Avoiding Cardiovascular Events through Combination Therapy in Patients Living with Systolic Hypertension (ACCOMPLISH) trial involves fixed-dose drug combinations in a double-blind clinical trial⁶ and is so far the only trial directly comparing two fixed combinations in all patients. This study found that ACE inhibitor+CCB had significant superiority over benazepril+thiazide diuretic, even in the elderly.⁶ In addition, the COLM study⁷ was a Prospective Randomized Open Blinded End point (PROBE) study with a response-dependent dose titration scheme in elderly Japanese high-risk hypertensive patients. In the COLM study, ARB was combined with CCB or thiazide diuretic and the safety and tolerability profiles observed suggested that ARB+CCB may be preferable to ARB+thiazide diuretic even at a very low dose.⁵ However, the COLM study was not able to detect statistically significant differences in the primary composite end points of cardiovascular morbidity and mortality, including renal events, between the two treatment arms due to the low incidence of cardiovascular events, as often occurs in clinical trials in Japan.^{8,9} The opposite conclusions with regard to the association of blood pressure control with clinical outcomes between the two trials may be explained by the differences in genetic background and/or lifestyle between Western countries and East Asian countries, especially Japan, where the incidence of cardiovascular events is lower and the incidence of stroke is higher than the incidence of coronary artery disease due to

the high salt intake.^{10,11} Furthermore, the difference in the study designs between the two studies, that is, the use of a double-blind fixed-dose combination study in the ACCOMPLISH trial⁶ vs. the use of a PROBE study involving two-drug combinations in the COLM study,⁷ may also have caused the differences in the reduction of cardiovascular events and in the safety profile.

Similarly, the OlmeSartan and Calcium Antagonists Randomized (OSCAR) study showed that ARB+CCB combination conferred greater benefit in preventing cardiovascular events in elderly patients than high-dose ARB alone.⁸ In contrast, in a sub-analysis of the Combination Therapy of Hypertension to Prevent Cardiovascular Events (COPE) trial comparing three combinations, that is, the combination of CCB with an ARB, a β -blocker or a thiazide diuretic,¹² little difference was observed in the primary cardiovascular events among the three treatment groups in elderly hypertensive patients. However, hyperuricemia and hypokalemia were more frequently reported in the benidipine–thiazide diuretic group and hyperkalemia was more frequently only in the benidipine–ARB group.

The adverse reactions associated with the combination treatments are mainly predicted from the known side effects of the individual drugs, and the decreased prevalence of symptoms and adverse metabolic effects with two-drug treatments in low-dose combinations and an increase in efficacy and a reduction in adverse drug reactions are also expected, as previously reported.¹ Several clinical trials performed in Japan, including the COLM study,^{5,7} indicate that CCB-based combination regimens are preferable, especially for elderly hypertensive patient safety.^{8,12} Taken together, these findings suggest that, mainly

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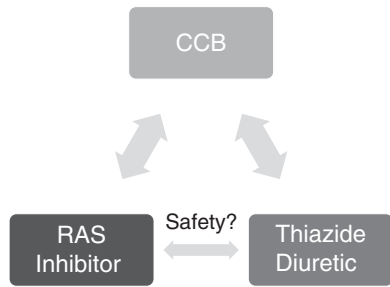


Figure 1 Combination of two drugs in the elderly. Angiotensin-converting enzyme (ACE) inhibitor or angiotensin receptor blocker (ARB)+CCB, ACE inhibitor or ARB+thiazide diuretic and CCB+thiazide diuretic are similarly effective in inhibiting the cardiovascular events and recommended as a combination therapy for the treatment of hypertension.¹ However, in this issue, the sub-analysis of the Combinations of Olmesartan study raised the concern about the safety and tolerability issue in the ARB and thiazide diuretic combination.⁵ RAS, renin-angiotensin system; CCB, calcium channel blocker. A full color version of this figure is available at *Hypertension Research* online.

from the viewpoint of the safety profile, CCB combined with thiazide diuretic or an ARB should be recommended as a combination treatment rather than the ARB-thiazide diuretic combination for elderly Japanese hypertensive patients (Figure 1).

Compliance with combination therapy is also important for achieving the target blood pressure and it may impact clinical outcomes.^{13,14} A large proportion of elderly patients will discontinue or take the drugs inappropriately; a drug's side-effect profile has been demonstrated to contribute to poor compliance.¹ The results of the safety profile in the COLM study^{5,7} are supported by the previous report,^{1,4} suggesting that the survival rates of patients prescribed CCBs and ARBs were similar and were the highest compared with other classes of drugs, probably due to the occurrence of fewer side effects. The prescription rates for other drug classes, except for thiazide diuretics, showed constant declines during the study period.⁴ In contrast, the cumulative rates of discontinuation of the study drugs were similar in the ACCOMPLISH trial.⁶ The most common reasons for discontinuation of the ACCOMPLISH trial medication were adverse events and laboratory test abnormalities, and the number of patients who permanently withdrew from the study was also similar in the two groups. The differences in compliance between the two studies may result from the study drugs or study designs, that is, the use of a double-blind study involving fixed-dose combination, ACE inhibitor with CCB or thiazide diuretic, in the ACCOMPLISH trial⁶ vs. the use of a PROBE study involving two-drug combinations, ARB with CCB or thiazide diuretic, in the COLM study.⁷ It is also possible that the

investigators' knowledge and the information bias related to a study drug influenced their safety reporting, even in a randomized and double-blinded design.¹⁵

Little evidence has been accumulated to determine which of two options, increasing the dosage of a single drug or introducing combination therapy with other drugs, should be selected as a therapeutic strategy for the treatment of hypertension in Japan. However, one of these options can be selected by considering the safety profile and likelihood of compliance and their compelling indications in addition to the clinical outcome for each antihypertensive drug under the physician's consideration.

CONFLICT OF INTEREST

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