COMMENTARY

Therapeutic impact of the single fixed-dose combination with a high-dose angiotensin-receptor blocker and a low-dose thiazide diuretic in the management of hypertension: awaiting further accumulation of clinical evidence

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Recently, major clinical guidelines for the treatment of hypertension have been revised in several countries.^{1–9} In these updated guidelines, five classes of antihypertensive drugs, including Ca^{2+} channel blockers, angiotensin receptor blockers (ARBs), angiotensin-converting enzyme (ACE) inhibitors, diuretics and β -blockers (including $\alpha\beta$ -blockers), were defined as major antihypertensive drugs, as they have been shown to prevent the occurrence of cardiovascular and renal events.¹⁰ In addition, among these five classes of antihypertensive drugs, Ca^{2+} channel blockers, ARBs, ACE inhibitors and low-dose thiazide-type diuretics were selected as first-choice drugs in hypertensive patients without specific conditions in the Japanese Society of Hypertension Guidelines for the Management of Hypertension (JSH 2014).⁹

If a condition is present for which antihypertensive therapy should be indicated, a single, condition-matched antihypertensive

drug or combination therapy may be considered with other classes of antihypertensive drugs. The most important aim of antihypertensive treatment is to prevent cardiovascular and renal events. Accumulated results of clinical trials, including meta-analyses, have shown that strict blood pressure (BP) control is essential to prevent target organ damage and to reduce cardiovascular mortality in hypertensive patients, and this preventive effect is proportionate to the degree of BP decrease rather than the class of antihypertensive drug used.¹¹ Thus, once antihypertensive drug therapy has been initiated, strict consideration for the achievement of target BP levels is critical in the treatment of hypertension. In the JSH 2014 guidelines,⁹ although antihypertensive drug therapy for grade I hypertension is recommended to be started with a single drug at a low dose, beginning antihypertensive drug therapy with a single drug at a standard dose or with a combination of two drugs at low doses for grade II or III hypertension is also recommended. Next, combination therapy with two or three drugs at standard doses, including single fixed-dose combinations, is recommended to achieve target BP control. A previous meta-analysis showed that the hypotensive effects of a combination of different classes of antihypertensive drugs were more marked than those of double-dose administration of the same drug.¹²

Evidence that strict BP control by combination therapy contributes to the further prevention of cardiovascular and renal events based on large-scale clinical studies is accumulating.

The ARBs and thiazide-type diuretics are first-choice antihypertensive drugs for hypertensive patients according to the JSH 2014 guidelines.⁹ ARBs are the second most common class of antihypertensive drugs in Japan, following Ca^{2+} channel blockers. It should also be noted that the Japanese diet is still characterized by a high salt intake, and salt-sensitive hypertension is common. In antihypertensive treatment, salt reduction is important, but a diuretic at a low dose may be used in hypertensive patients in whom salt restriction is difficult. In addition, in large-scale clinical studies, the proportion of patients taking a diuretic in addition to other classes of antihypertensive drugs was also high, and even diuretic monotherapy prevented cardiovascular events.^{13,14} Therefore, combination therapy with two or three drugs, including ARBs and diuretics, is likely to be effective in achieving target BP and preventing cardiovascular events in many hypertensive patients.

Furthermore, a reduction in the number of tablets to be taken and simplification of the prescription through the use of fixed-combination drugs is advantageous for improving adherence.⁹ A meta-analysis showed that fixed-combination drugs exhibited more

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Figure 1 Summary of the recommended management of hypertension with CKD in Japan. ABPM, ambulatory blood pressure monitoring; ACE inhibitors, angiotensin-converting enzyme inhibitors; ARB, angiotensin receptor blocker; BP, blood pressure; CCB, Ca^{2+} channel blocker; CGA, Cause, GFR and Albuminuria categories; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; HBPM, home blood pressure monitoring. A full color version of this figure is available at the *Hypertension Research* journal online.

potent hypotensive effects than combination therapy with respective drugs by improving adherence and that these drugs improved the rate at which target BP control is achieved.¹⁵ As the dose of a fixed-combination drug is fixed and initial administration may cause an excessive BP decrease, administration of fixed-combination drugs should be a second or third step in achieving target BP control, after establishment of the dose/doses by the initial administration of a single drug or a combination of two drugs.⁹ In Japan, fixed-combination drugs of an ARB and a diuretic and those of an ARB and a Ca^{2+} channel blocker are currently available.

In this issue, Rakugi *et al.*¹⁶ examined the safety, tolerability and efficacy on clinic BP management of high-dose losartan (losartan 100 mg; L100) plus a low-dose thiazide diuretic (hydrochlorothiazide 12.5 mg; H12.5) in a single fixed-dose combination in hypertensive patients in two randomized studies. In the first study (L50/H12.5 filter study), hypertensive patients received losartan 50 mg (L50) plus H12.5 during an 8-week filter period. They were then randomized to either L100/H12.5 or L50/H12.5 for another 8 weeks, followed by L100/H12.5 for 44 weeks. In the second study (L100 filter study), hypertensive patients received L100 during an 8-week filter period. Subjects were then randomized to

receive either L100/H12.5 or L100 for a further 8 weeks.

In the first L50/H12.5 filter study, the differences between L100/H12.5 and L50/H12.5 in change from baseline to week 8 for diastolic BP was 0.2 mmHg ($P=0.6590$) and for systolic BP was -2.3 mmHg ($P=0.0317$), showing that L100/H12.5 may exert a marginally additive BP-lowering effect over L50/H12.5 in hypertensive patients.¹⁶ In the L100 filter study, the differences between L100/H12.5 and L100 in change from baseline to week 8 for diastolic BP was -5.1 mmHg ($P<0.001$) and for systolic BP was -9.2 mmHg ($P<0.001$), demonstrating that the addition of low-dose diuretics significantly enhanced the ARB-mediated BP-lowering effect in hypertensive patients.¹⁶ In addition, the safety and tolerability of L100/H12.5 were favorable and comparable to L50/H12.5, and long-term analysis demonstrated that L100/H12.5 was generally well tolerated in the L50/H12.5 and L100/H12.5 filter studies. It was also noted that uric acid levels were significantly reduced with long-term treatment with L100/H12.5 in subjects whose baseline uric acid level was >7.0 mg/dl.¹⁶

These results indicate that a single fixed-dose combination with an ARB and a diuretic is advantageous, not only because of the synergism of hypotensive effects but also

because of the offset of adverse effects on electrolyte and glucose metabolism. With respect to the comparison of therapeutic efficacy between an ARB–diuretic combination and an ARB– Ca^{2+} channel blocker combination for the treatment of hypertension, in a large-scale, randomized, double-blind study (ACCOMPLISH), combination therapy with an ACE inhibitor and a Ca^{2+} channel blocker was more effective at preventing the occurrence of cardiovascular events and death in comparison with an ACE inhibitor and a diuretic.¹⁷ In addition, a prespecified sub-analysis of ACCOMPLISH study in high-risk hypertensive patients with chronic kidney disease (CKD) (ACCOMPLISH-CKD study) showed that the urinary albumin-decreasing effects of combination therapy with an ACE inhibitor and a diuretic were superior to those of an ACE inhibitor and a Ca^{2+} channel blocker, but the preventive effects of the latter on the progression of CKD were more potent than those of the former.¹⁸ However, in a *post-hoc* sub-analysis of the ACCOMPLISH-CKD study, there were no significant differences in slowing the progression of CKD and in reducing cardiovascular events in diabetic nephropathy patients between the two combination therapies.¹⁸ On the basis of these results, in the Evidence-Based Clinical Practice Guideline for CKD 2013 and JSH

2014, it is recommended that an ARB or ACE inhibitor should be combined with a diuretic in hypertensive CKD patients with fluid retention (Figure 1).^{8,9} Therefore further clinical evidence is necessary to establish the therapeutic benefit of combination therapy including single fixed-dose combinations with an ARB and a diuretic in terms of achieving more efficient suppressive effects on cardiovascular and renal events in hypertension, in particular, in high-risk hypertension such as hypertension complicated with CKD and/or diabetes.¹⁹⁻²²

CONFLICT OF INTEREST

K Tamura received honoraria, consulting fees or funds from Mochida, Daiichi-Sankyo, Dainippon-Sumitomo, Novartis, Takeda, MSD, Kyowa-hakko Kirin, Shionogi, Boehringer Ingelheim, Astellas, Tanabe Mitsubishi, Pfizer, Chu-gai, AstraZeneca and Sanofi. S Umemura received honoraria, consulting fees or funds from Shionogi, Astellas, Torii, Dainippon-Sumitomo, Boehringer Ingelheim, MSD, Pfizer, Daiichi-Sankyo, Novartis, AstraZeneca, Takeda, Kyowa-hakko Kirin, Kowasoyaku, Acterion, Otsuka, Bayer, Chugai, Mochida, Tanabe Mitsubishi, Teijin, Sanofi and Sanwa-kagaku. The remaining authors declare no conflict of interest.

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