

## COMMENTARY

# Are diuretic additives fit for uncontrolled hypertensive patients receiving telmisartan and amlodipine treatment?

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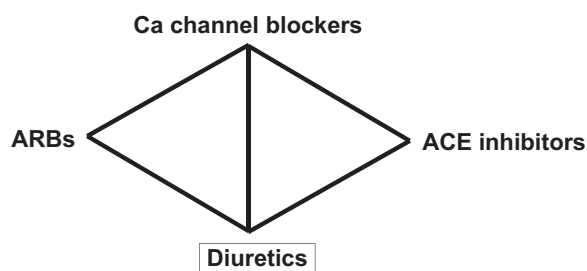
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Hypertension is prevalent in the adult population within Japan, especially among men over 50 years of age and women over 60 years of age.<sup>1</sup> Forty-three million adults in Japan and ~1 billion adults worldwide have high blood pressure. Hypertension is considered to be strongly associated with cardiovascular diseases including stroke, myocardial infarction and heart failure. Treatment of hypertension can reduce the risk of these diseases, and targeting systolic pressure will be discussed herein. A recent clinical trial, SPRINT,<sup>2</sup> demonstrated that targeting a systolic blood pressure of <120 mm Hg, compared with <140 mm Hg, resulted in fewer fatal and nonfatal major cardiovascular events and death from any cause among patients without diabetes who are at a high risk for cardiovascular events. Targeting a systolic blood pressure of <120 mm Hg greatly reduced the rate of heart failure and death from cardiovascular events.<sup>2</sup> In the SPRINT trial, the results showed that diuretics such as thiazides are broadly recommended, and diuretics may reduce the occurrence of heart failure. Although the SPRINT trial includes important data on target systolic blood pressures for Americans that could apply to the Japanese population, physicians need to thoroughly consider the differences between the two populations before broadly applying these blood pressure criteria to Japanese patients. The beneficial effect of diuretics, such as thiazide, was also recognized in the ALLHAT trial.<sup>3</sup> The diuretic

effect of the SGLT2 inhibitor empagliflozin may reduce cardiovascular events, as shown in the EMPA-REG OUTCOME trial.<sup>4</sup> The neprilysin inhibitor of LCZ696 may reduce the risk of death and hospitalization for heart failure through its diuretic effect as shown in the PARADIGM-HF trial.<sup>5</sup> In addition, a meta-analysis of randomized controlled trials from 1997 through 2009 published in the PubMed and EMBASE database ( $n=223\ 313$ ) indicates that diuretics is the most effective class of drugs in preventing heart failure, followed by renin–angiotensin inhibitors.<sup>6</sup> Overall, diuretics are currently being reassessed for the treatment of hypertensive patients.

Of note, Higaki *et al.*<sup>7</sup> reported a clinical trial in Japan regarding diuretic additives entitled ‘The efficacy and long-term safety of a triple combination of 80 mg telmisartan, 5 mg amlodipine and 12.5 mg hydrochlorothiazide in Japanese patients with essential hypertension: a randomized, double-blind study with open-label extension’. The trial demonstrated that the combination

of telmisartan, amlodipine and diuretics (hydrochlorothiazide;  $n=149$ ) is more effective than the combination of telmisartan and amlodipine ( $n=160$ ) at reducing blood pressure in hypertensive patients after 8 weeks of treatment (–5.6 mm Hg for systolic pressure and –4.0 mm Hg for diastolic pressure). The result of this study is consistent with a previous report.<sup>8</sup> According to the Japanese Society of Hypertension Guidelines for the Management of Hypertension (JSH 2014),<sup>1</sup> angiotensin II receptor blockers (ARBs), angiotensin-converting enzyme (ACE) inhibitors, calcium channel blockers and diuretics are all first-line drugs for treating hypertension. As shown in Figure 1,<sup>1</sup> combination therapies of calcium channel blockers and ARBs/ACE inhibitors, diuretics and ARBs/ACE inhibitors, and calcium channel blockers and diuretics are recommended. We should decide on utilizing one of these combinations according to the differences in patient backgrounds and the results of previous clinical trials. For example, Saruta *et al.*<sup>9</sup> demonstrated in the COLM trial that ARBs



**Figure 1** Angiotensin II receptor blockers (ARBs), angiotensin-converting enzyme (ACE) inhibitors, calcium channel blockers and diuretics are all first-line drugs for treating hypertension. Combination therapies of calcium channel blockers and ARBs/ACE inhibitors, diuretics and ARBs/ACE inhibitors, or calcium channel blockers and diuretics are recommended. Figure 1 expresses these concepts and is modified from JSH 2014, combination of anti-hypertensive drug.<sup>1</sup>

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and calcium channel blockers are superior to ARBs and diuretics in terms of adverse events for elderly hypertensive patients aged 65–84 years. In any case, the administration of diuretics should be attempted first for patients whose blood pressure is not controlled with ARBs/ACE inhibitors and calcium channel blocker treatment; the strategy of this clinical trial is reasonable.

Higaki *et al.*<sup>7</sup> reported that an elevated blood uric acid level and hyperuricemia are more frequent when the combination of telmisartan, amlodipine and hydrochlorothiazide is administered compared with that of telmisartan and amlodipine. These adverse events have also been observed in a previous study.<sup>8</sup> However, these adverse events are common, and the side effects of diuretics are manageable. In this study, serum sodium and potassium were not significantly different between the two groups, but we should continue to monitor serum electrolytes, hydration status and renal function.

There are several limitations to the study by Higaki *et al.*<sup>7</sup> For example, the patient follow-up period was relatively short, and the sample size of patients was small. With consideration of these limitations, the addition of diuretics (hydrochlorothiazide) to the anti-hypertensive regimen for uncontrolled Japanese hypertensive patients taking ARBs

and calcium channel blockers is effective and well tolerated.

#### CONFLICT OF INTEREST

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