Hypertension is one of the major risk factors of cardiovascular diseases. In Japan as well as in Western countries, the number of obese individuals with hypertension has been rapidly increasing. It has been demonstrated that visceral obesity causes qualitative and quantitative abnormalities in adipokines, thus leading to the condition that is defined as metabolic syndrome. The main aim of lowering blood pressure is to prevent cardiovascular diseases. The results of previous trials indicate that the amount of blood pressure reduction, not the class of drugs, is the major determinant of reduction in cardiovascular risk; all the antihypertensive drugs have both positive indications and contraindications according to the condition under which they are used. Therefore, appropriate antihypertensive drugs should be selected based on various factors, including positive indications, conditions that require careful use of drugs and the presence or absence of complications. The Japanese guideline of JSH 2009 recommends that the antihypertensive drugs primarily administered to patients with diabetes mellitus and metabolic syndrome should be selected from angiotensin-converting enzyme inhibitors (ACEI) or angiotensin-receptor blockers (ARB). In case an amount of one class of antihypertensive drug is not sufficient to lower blood pressure, the dose should be increased or a low dose of an antihypertensive drug from a different class should be used concomitantly. However, there is not a lot of evidence as to which combination is better than other combinations in a specific condition such as metabolic syndrome.

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In this issue of Circulation Journal, Huang et al provides some evidence that antihypertensive combination therapy including diuretics, even if its dosage is half as much as normal therapeutic dosage, might cause adverse effect on metabolism, which offsets the ameliorating effect of an ACEI on metabolism. The authors evaluated the effect of a combination therapy of an ACEI and a thiazide-like diuretic and monotherapy of an ACEI on plasma adiponectin concentrations in patients with essential hypertension. Thirty patients were randomized to receive a fixed-dose combination therapy of ACEI and thiazide diuretics or ACEI monotherapy. The enrolled participants had increased body mass index and fasting glucose and decreased high-density lipoprotein cholesterol concentration, characteristics of metabolic syndrome. While treatment with an ACEI alone increased adiponectin concentrations significantly, combination of an ACEI with low-dose thiazide diuretics did not alter the adiponectin concentration but increased insulin resistance index.

Adiponectin is an adipocyte-derived insulin sensitizer. Individuals with high concentrations of blood adiponectin were less likely to develop type 2 diabetes than those with low concentrations, even after adjustment for glucose levels. Adiponectin has direct anti-inflammatory effect on the heart and blood vessel cells. High plasma adiponectin concentrations are associated with a lower risk of myocardial infarction after adjustment for conventional risk factors. Previous studies reported that plasma adiponectin concentration is differentially influenced by different classes of antihypertensive drugs. ACEI and ARB, which improve insulin sensitivities, have been reported to increase blood adiponectin concentrations. It is also reported that ARB reduced the incidence of new-onset diabetes. Moreover, the effects on plasma adiponectin concentrations of these drugs parallel their effects on blood pressure and insulin sensitivities. In contrast, thiazides and thiazide-like diuretics are known to enhance insulin resistance and worsen glycemic control. A thiazide-like diuretic, indapamide, has been reported to decrease blood adiponectin concentration, explaining the cause of metabolic disturbances often found in patients treated with thiazide-type diuretics. The present study by Huang et al clearly demonstrated that hypertensive drugs have interacting and offsetting effects on blood adiponectin and metabolism.

The present study has several limitations. The present study evaluated only the surrogate marker of cardiovascular diseases. Further studies will be needed to clarify the net effect of combination therapy of ACEI and diuretics on prevention of cardiovascular diseases. In this sense, the recent ACCOMPLISH trial provides some evidence. ACCOMPLISH tested whether a combination therapy of an ACEI benazepril with amlodipine is superior in the cardiovascular outcomes to a combination therapy of the same ACEI combined with a thiazide diuretic. The benazepril-amlodipine group had a significantly reduced risk of cardiovascular events compared with the benazepril-hydrochlorothiazide group. The benazepril-amlodipine group had slightly lower mean blood pressure than the benazepril-hydrochlorothiazide group. However, the 24-h, daytime and night-time average blood pressure has been reported to be similar in both groups, indicating that the benefits with the benazepril-amlodipine combination is unlikely to be...
due to better blood pressure control. It is possible that there might be an adverse effect of hydrochlorothiazide, although the possibility that a synergistic effect of an ACEI and amlopidine on nitric oxide exerted a beneficial effect to slow the progression of atherosclerotic lesions cannot be excluded. In Japan, the COLM trial, which is in progress, is comparing ARB plus diuretic with ARB plus Ca channel blocker regarding the morbidity and mortality of cardiovascular disease.13 Along with the COPE, which compares Ca channel blocker plus diuretic and Ca channel blocker plus β-blocker with Ca channel blocker plus ARB,14 the results are awaited.

Adiponectin exists in 3 major oligomeric forms. Among these 3 forms, high-molecular weight (HMW) adiponectin is the most potent in sensitizing insulin action in peripheral tissue and correlates well with the improvement in insulin sensitivity during treatment by drugs such as TZD.1 It is also reported that HMW adiponectin and the HMW-to-total adiponectin ratio have significantly better power for the prediction of insulin resistance and the metabolic syndrome in humans.1 Thus, measuring the HMW adiponectin concentration before and after the use of hypertensive drug would be interesting for the evaluation of its beneficial or adverse effect on metabolism.

The seventh report of the JNC 7 guidelines recommend that thiazide diuretics be included in combination regimens. The Japanese guideline of JSH 2009 points out that diuretics are expected to be particularly effective in patients with increased salt sensitivity, such as the elderly, and in patients with low renin hypertension.3 Additionally, it has been pointed out that adverse effect of diuretics on glucose tolerance and metabolism can be minimized without marked attenuation of the hypotensive effect by using diuretics at a low dose.3 ADVANCE, which compared the effects of a fixed-combination drug of an ACEI and diuretic with a placebo in diabetic patients, indicated the usefulness of the fixed-combination drug.15 However, the study by Huang et al suggested that even a small dose of diuretics might have adverse effect on glucose metabolism. Taken together with the result of ACCOMPLISH, Ca-blocker might have better effect on patients if it is combined with an ACEI but not with thiazide diuretics, especially for patients with diabetes or metabolic syndrome and a low concentration of blood adiponectin. The number of obese individuals with hypertension has been rapidly increasing and up to 50% of the hypertensive patients might have metabolic syndrome by definition. The result of this study could be applied to most of the cases with hypertension. Many of the fixed-combination drugs marketed so far include diuretics. But a fixed-combination drug of an ARB and a Ca channel blocker, which will also be marketed soon in Japan, might be another good option for some patients with hypertension and obesity.

The present study emphasizes the importance of considering beneficial and adverse impact of antihypertensive drugs on glucose metabolism in addition to their blood pressure lowering effect in the treatment of hypertension. The results of randomized trials which evaluate the difference in cardiovascular outcomes between different combination therapy of hypertension will be awaited. It is of note to confirm the relationship between the alteration in surrogate markers and cardiovascular outcomes. We should now choose the best combination of antihypertensive drugs to treat hypertension beyond lowering blood pressure.

References