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COMMENTARY

Benefits and risks of combination therapy in hypertension

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Strict blood pressure control is one of the best strategies for preventing myocardial infarction and stroke. However, it is difficult to lower blood pressure in high-risk patients in terms of 24 h blood pressure control. An increase in the dose of antihypertensive drugs or combination therapy are both effective tools for obtaining good control in such patients, with combination therapy generally being the more effective option in these cases.

Many patients with essential hypertension will require two or more drugs that have complementary mechanisms of action. Such a strategy would be expected to optimize blood pressure control while minimizing the incidence of adverse events.

Angiotensin II type 1 (AT1) receptor blockers (ARBs), which act by selectively blocking the binding of angiotensin II to the AT1 receptor, are used widely in the treatment of hypertension. These agents have benefits beyond blood pressure control, with evidence that they also have cardiovascular, cerebral and renal protective effects, as a consequence of inhibition of renin–angiotensin activation at the tissue level and also autocrine/paracrine effects. In addition to direct end-organ protection, some ARBs improve abnormalities in glucose and lipid metabolism, resulting in an antiatherosclerotic effect.

Two randomized prospective trials, LIFE and RENAL, provided evidence on the effect of combination therapy with an ARB, angiotensin-converting enzyme (ACE) inhibitor and low-dose diuretic on cardiovascular events including total mortality. Several other clinical studies have also supported the efficacy and safety of combination therapy with renin-angiotensin system inhibitors and a low dose of diuretics.

In addition to lowering the blood pressure, ACE inhibitors in combination with low-dose diuretics have been shown to improve vascular endothelial and smooth muscle function. Similar effects have been shown with ARBs and lower doses of diuretics.

Several mechanisms are involved in the pathogenesis of hypertension. Combinations of antihypertensive drugs with complementary mechanisms of action may therefore affect more than one physiological pathway, with resulting synergistic effects on blood pressure. Moreover, combination therapy increases patient drug compliance.

Certain patient populations appear to derive particular therapeutic benefit from specific combinations of antihypertensive agents. For example, the addition of diuretics to a β-blocker, ACE inhibitor or ARB is especially effective in salt-sensitive hypertensive patients. However, in patients with augmented stiffness of smooth muscle, a combination of an ARB and calcium channel blocker may be more effective for reducing blood pressure. Certainly, the combination effect on the degree of blood pressure reduction depends on the dose of each drug.

Combination therapy with ARBs and lower doses of diuretics provides cost benefits.

The cost of a fixed-dose combination of a diuretic with either a β-blocker, ACE inhibitor or ARB is typically no higher than that for a non-diuretic drug alone. Therefore, such combinations will produce greater reductions in blood pressure and higher response rates at minimal cost.

Improvement in patient compliance also reduces the incidence of complications relating to hypertensive target organ damage and lowers the cost of management of such events, which may include hospitalization.

Recently, the 2009 JSH guidelines recommended the combination therapies of ARBs and diuretics, ARBs and calcium channel blockers and calcium channel blockers and diuretics, on the basis of their efficacy, safety and compliance ratings. These guidelines also reported that combined therapy with ARBs and diuretics was especially beneficial for reducing blood pressure at night and in the early morning.

On the other hand, the CAMELOT and NOMALIZE trials provided strong clinical evidence that calcium channel blockers, including amlodipine, reduced cardiac events as a result of plaque stabilization. Therefore, there are many cases of patients with coronary artery disease in whom amlodipine should be used to obtain strict blood pressure control and improve vascular function, including the inhibition of vascular spasm.

It remains controversial whether a combination of an ARB and a diuretic is better than an ARB and a calcium channel blocker for achieving blood pressure control.

Telmisartan plus hydrochlorothiazide antihypertensive therapy has a different effect on blood pressure, and is also reported to be safe with less side effects.

Telmisartan is an ARB that is highly selective for the AT1 receptor and has a long duration of action because of its long terminal elimination half-life. In addition to antagonizing AT1 receptors, telmisartan has the unique property of activating peroxisome proliferator-activated receptor-γ, thereby improving insulin sensitivity, reducing triglyceride levels and increasing adiponectin levels. These effects may improve metabolic syndrome characteristics and thereby reduce the risk of atherosclerosis.

In this issue, Ando *et al.*[1] show that combination therapy with an inhibitor of the renin–angiotensin system and a

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low-dose thiazide is useful in cases in whom a calcium channel blocker was not achieving adequate control of hypertension. This result suggests that in patients with uncontrolled hypertension following treatment with amlodipine monotherapy, one strategy to achieve target blood pressure control is to change to a combined therapy with telmisartan and low-dose hydrochlorothiazide.

In patients with salt insensitivity, thiazide diuretics induce a greater reduction in blood pressure than a calcium channel blocker. It is therefore necessary to clarify the background of patients with and without salt insensitivity.

It has been reported that there are some differences in the effect on serum uric acid levels caused by different ARBs. We therefore need to clarify the different beneficial and adverse side effects associated with different combinations of ARBs and diuretics.

In this protocol, there were no significant differences in glucose and lipid profiles between the two groups after 12 weeks. However, it still remains to be established if this similarity persisted for longer periods.

It is therefore necessary to examine the long-term inhibitory effects of these combined therapies on cardiovascular factors. The primary end point for the treatment of hypertension is the prevention of cardiovascular, cerebral and renal complications. Although hypertension is a major atherogenic risk factor, it never occurs independent of other risk factors. Accordingly, we should focus on the effect of combination therapy on long-term cardiovascular events and comprehensively treat all risk factors, including hypertension, abnormal glucose or lipid metabolism, and clusters of risk factors such as the metabolic syndrome using a combination of appropriate antihypertensive drugs.

1 Ando K, Isshiki M, Takahashi K. Effect of switching from amlodipine to combination therapy with telmisartan and low-dose hydrochlorothiazide. *Hypertens Res* 2009; **32**: 748–752.