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COMMENTARY

The ideal combination of anti-hypertensive drugs

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The history of antihypertensive therapy extends over half a century, during which time numerous clinical studies have established that strict control of blood pressure results in maximum benefits to hypertensive patients. This strategy represents the established dogma of antihypertensive therapy 'the lower, the better'. However, there is evidence that over 60% of patients on single-drug therapy may fail to attain blood pressure goals. The recently published guidelines for treating hypertension, including the JSH2009, have recommended a combination therapy of antihypertensive drugs.[1] However, it has not been confirmed which drug combination is the most effective. Angiotensin type 1 receptor blockers (ARBs) and calcium channel blockers (CCBs) are both widely prescribed drugs in Japan and Western countries. Both drugs provide target-organ protection owing to their antihypertensive action, and also have additional beneficial effects over and above their blood-pressure-lowering action. For example, ARBs have actions that prevent the onset of diabetes mellitus, decrease hospital admissions due to heart failure and preserve, or even improve, renal function. As a consequence, ARBs are often prescribed in industrialized countries in an era of increasing metabolic diseases that are associated with numerous co-morbidities. Examples of the pleiotropic effects of long-acting dihydropiridine CCBs include regression of left-ventricular hypertrophy and a suggested anti-atherosclerotic action on blood vessels.

In this issue, Ogihara *et al.*[2] report the results of a randomized, double-blind, four-arm parallel-group study in hypertensive patients on the efficacy and safety of azelnidipine and olmesartan medoxomil combination therapy compared with each monotherapy. Azelnidipine is a long-acting dihydropiridine CCB with a strong antihypertensive action that is achieved gradually by high membrane penetration (that is, a 'membrane approach'), suppression of sympathetic overdrive and a potential antioxidative action on membranes of blood vessels. This particular action of azelnidipine results in decreased intraglomerular hypertension and thus decreased urinary protein excretion, and improved diastolic function in patients with heart failure.[3] On the other hand, olmesartan is a highly effective angiotensin type II receptor blocker with ultra-high-affinity double anchor domains to the angiotensin II type 1 receptor. Ogihara *et al.*[2] showed a combination of olmesartan 20 mg with azelnidipine 16 mg caused a maximum reduction in systolic blood pressure of 23.6 mm Hg and in diastolic blood pressure of 14.2 mm Hg. Ambulatory blood pressure monitoring in these patients also showed a reduction of 22.1 and 13.5 mm Hg in systolic and diastolic pressure, respectively. No significant adverse effects of this combination therapy were observed. The authors therefore concluded that the combination therapy of azelnidipine and olmesartan was a highly effective antihypertensive regimen with good tolerability.

It has yet to be established whether CCBs are a better combination with ARB than diuretics. To obtain this information, a large randomized controlled trial, COLM, is currently being carried out in Japan.[4] Previously, the ACCOMPLISH study compared the efficacy of combination therapy using either CCBs or diuretics with that using an angiotensin-converting enzyme inhibitor, and showed that the CCB-based combined therapy was the best.[5] In Japan, the results of comparison of ordinary therapy, mainly CCBs, and this therapy in combination with an ARB have been reported. The E-COST,[6] JIKEI study[7] and the Kyoto Heart Study[8] have all reported that addition of ARB decreased the incidence of cardiovascular events. These findings suggest that ARBs and CCBs are an excellent combination for treatment of hypertensive patients.[9] Therefore, combined azelnidipine and olmesartan may be a particularly useful regimen in these patients.

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