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Combination Therapy for Treatment or Prevention of Atherosclerosis

To the Editor:
Nakamura et al.1 investigated the effects of pioglitazone, a peroxisome proliferator-activated receptor (PPAR)-γ agonist, candesartan, or combination therapy on hypertensive cardiovascular injury. They found that candesartan or pioglitazone protects against hypertensive cardiovascular damage without lowering blood pressure, whereas combination therapy exerts greater beneficial effects than monotherapy with either drug on hypertensive cardiovascular injury by suppressing reactive oxygen species to a greater extent. The authors conclude that combination therapy is important in the treatment of cardiovascular disease, including hypertension with type 2 diabetes.

The additional beneficial effects of combined pioglitazone/candesartan therapy may be the result of several interacting mechanisms.2 Indeed, recent experimental studies have demonstrated cross-talk between PPAR-α or PPAR-γ and angiotensin II.3–5 Angiotensin II binds to angiotensin II type I receptor, which produces oxygen free radicals by using reduced nicotinamide adenine dinucleotide/reduced nicotinamide adenine dinucleotide phosphate oxidase. Oxygen free radicals activate nuclear factor κB and stimulate proinflammatory gene expression. Angiotensin II also downregulates the expression of PPAR-α and PPAR-γ. This promotes vascular inflammation and acceleration of atherosclerosis in apolipoprotein E knockout mice.5 Angiotensin II type I receptor blockers modulate this process by inhibiting nuclear factor κB by oxygen free radicals.2 PPAR-γ ligands (thiazolidinediones) suppress the expression of angiotensin II type I receptor messenger RNA and protein.4 Thus, PPAR-γ ligands may inhibit angiotensin II–induced cell growth and hypertrophy in vascular smooth muscle cells by suppressing angiotensin II type I receptor expression. Angiotensin II type I receptor blockers induce PPAR-γ activity, thereby promoting PPAR-γ–dependent differentiation in adipocytes. The activation of PPAR-γ provides a potential mechanism for insulin-sensitizing/antidiabetic effects of angiotensin II type I receptor blockers.3 Therefore, combination therapy with pioglitazone or fenofibrate and candesartan may determine greater beneficial effects than monotherapy by both distinct and interrelated mechanisms.

Combined therapy may be beneficial for the treatment of diabetic patients with hypertension and atherosclerosis or hypertriglyceridemic and hypertensive patients. We investigated vascular and metabolic responses to either 200 mg of fenofibrate or 16 mg of candesartan alone or in combination in hypertriglyceridemic, hypertensive patients. Combined therapy significantly reduces blood pressure more than fenofibrate or candesartan alone. When compared with candesartan, fenofibrate or combined therapy significantly improves the lipoprotein profile. Combined therapy significantly decreases plasma malondialdehyde, high sensitivity C-reactive protein, and soluble CD40L levels and improves the flow-mediated dilator response to hyperemia to a greater extent than monotherapy. Fenofibrate combined with candesartan improves endothelial function and reduces inflammatory markers to a greater extent than monotherapy in hypertriglyceridemic, hypertensive patients.6 Thus, there is a strong and growing scientific rationale for recommending a combination of PPAR-α or PPAR-γ and angiotensin II type I receptor blockers to prevent atherosclerosis and coronary heart disease.2

Disclosures

None.

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