Systemic hypertension, hypercholesterolaemia and diabetes are associated with endothelial dysfunction that promotes inflammation, oxidation of lipoproteins, smooth-muscle proliferation, extracellular matrix deposition or lysis, accumulation of lipid-rich material, platelet activation, thrombus formation and insulin resistance. All of these consequences of endothelial dysfunction and insulin resistance may contribute to the development and clinical expression of atherosclerosis.1 Hypercholesterolaemia and hypertension are major public health problems that are frequently treated with statins and renin-angiotensin system (RAS) blockades. Although the mechanisms of action for these two classes of drugs differ, both classes have beneficial effects on the vasculature. Experimental and clinical studies demonstrated that combined statins and RAS blockades improve endothelial function as reflected by improved flow-mediated dilation, improved fibrolysis potential and reduced oxidant stress, inflammatory markers and insulin sensitivity. There is a strong scientific rationale for recommending combination therapy, especially statins and RAS blockades, to treat or prevent atherosclerosis and coronary heart disease. In this article, we address the mechanisms on the cross-talk between statins and RAS and discuss the rationale and importance of combination therapy with statins and RAS blockades in treating and preventing cardiovascular events.

Basic Mechanisms and Pre-clinical Evidence In Terms of Cross-talk Between Statin and the Renin-angiotensin System

Statins reduce low-density lipoprotein (LDL) cholesterol and improve endothelial function via stimulation of nitric oxide (NO) synthase activity, and mediate antioxidant effects that result in enhanced NO bioactivity.7,8 In addition, statins have antioxidative effects via indirect NO inhibitory action through inhibition of Rac isoprenylation and attenuate oxidative stress through inhibition of Rac.17 Atorvastatin protects against cerebral infarction via inhibition of nicotinamide adenine dinucleotide phosphate (NADPH) oxidase-derived superoxide in transient focal ischaemia.16 Cerivastatin may act by inhibiting the prenylation, membrane anchoring and subsequent activation of Ras proteins.18 Lovastatin also stimulates protein kinase B/Akt kinase activity, and Akt-dependent phosphorylation forces p21 in the cytoplasm where it inhibits Rho-kinases contributing to the suppression of cardiomyocyte hypertrophy.19

RAS blockades also improve endothelial function.10,11 A potential mechanism of this effect is augmented NO bioactivity via diminished bradykinin degradation by angiotensin-converting enzyme (ACE) with activation of endothelial B2 kinin receptors and stimulation of NO synthase activity.11 Alternatively, ACE inhibition may diminish intracellular production of superoxide anions via reduced activity of angiotensin II-dependent oxidases in the endothelium and vascular smooth muscle,14–17 thus protecting NO from oxidant degradation to biologically inert or toxic molecules.18 Inhibition of the production of superoxide anions may also limit the oxidation of LDL, thus contributing to increased NO bioactivity by enhancing NO synthesis and limiting oxidative degradation of NO.19–21 These studies suggest that angiotensin II promotes superoxide anion generation and endothelial dysfunction. This effect is mediated by the angiotensin II type 1 (AT1) receptor. Angiotensin II activates the nuclear transcription factor nuclear factor kappa B (NFκB), which is induced by oxidative stress.22 NFκB activates pro-inflammatory transcription factors and thus stimulates the synthesis of protein products, such as cell adhesion molecules and chemokines.23–25 On the other hand, angiotensin II
We reported additive beneficial effects of combined therapy with statins and the Renin-angiotensin System (RAS) blockades on vascular and metabolic responses. The additional beneficial effects of combined statins and RAS blockades may be the result of several interacting mechanisms. For example, angiotensin II is a potent endogenous vasoconstrictor, while LDL receptors inhibit LDL oxidation and attenuate atherosclerosis. 24 The combined therapy with simvastatin and losartan significantly improved the flow-mediated dilation response to hyperaemia (A), malondialdehyde levels (MDLs) (oxidative stress marker) (B) and monocyte chemoattractant protein-1 (MCP-1) (inflammatory marker) (C) compared with simvastatin and losartan alone in hypercholesterolaemic hypertensive patients. 25 ANOVA = analysis of variance.

Compared with those of either statin and RAS blockade alone in patients with cardiovascular risk factors. 26 Losartan alone, simvastatin alone or combined therapy with losartan and simvastatin significantly improved flow-mediated dilator response to hyperaemia (marker of endothelial function) and decreased plasma oxidant stress and inflammatory marker relative to baseline measurements. However, these parameters were changed to a greater extent with combined therapy compared with simvastatin or losartan alone (see Figure 2). Of interest, combined therapy or losartan alone

The combined therapy with simvastatin and losartan significantly improved the flow-mediated dilation response to hyperaemia (A), malondialdehyde levels (MDLs) (oxidative stress marker) (B) and monocyte chemoattractant protein-1 (MCP-1) (inflammatory marker) (C) compared with simvastatin and losartan alone in hypercholesterolaemic hypertensive patients. 25 ANOVA = analysis of variance.

In experimental studies with endothelial cells in culture, many stimuli initiate transcription of genes that encode protein mediators of inflammation. Dysregulation of the renin-angiotensin system (RAS) may contribute to the pathogenesis of atherosclerosis. Angiotensin II binds to angiotensin II type I receptor (AT1R) resulting in enzymatic production of oxygen-derived free radicals. This leads to dissociation of inhibitory factor IκB, with subsequent activation of nuclear factor kappa B (NF-κB) that stimulates expression of pro-inflammatory genes, chemokines and cytokines. Statins may modulate this process by inhibiting the activation of nuclear transcription factors. Low-density lipoprotein (LDL) induces upregulation of the AT1R. The effect of statins to reverse the elevated blood pressure response to angiotensin II infusion is accompanied by downregulated AT1 receptor density. This figure may help to explain why combined therapy with statins and RAS blockades have additive beneficial effects on endothelial dysfunction compared with monotherapies in patients with cardiovascular risk factors. 27 ACEIs = angiotensin-converting enzyme inhibitors; ARBs = angiotensin II type 1 receptor blockers; CAM-1 = inter-cellular adhesion molecule-1; FFA = free fatty acid; HDL = high-density lipoprotein; ILKβ = inhibitor of nuclear factor kappa-B kinase subunit beta; NF-κB = nuclear factor kappa-B; MCP-1 = monocyte chemoattractant protein-1; M-CSF = macrophage colony-stimulating factor; NADPH = nicotinamide adenine dinucleotide phosphate; NO = nitric oxide; PAI-1 = plasminogen activator inhibitor-1; SOD = superoxide dismutase; VCAM-1 = vascular cell adhesion molecule-1; CRP = C-reactive protein

Clustering of inflammatory and metabolic risk factors is associated with increased risk of cardiovascular disease. 28, 29 Therapy with both drugs decreases plaque area and lipid deposition after 10 weeks. 29 The additional beneficial effects of combined statins and RAS blockades may be the result of several interacting mechanisms. For example, angiotensin II is a potent endogenous vasoconstrictor, while LDL induces upregulation of the AT1 receptor. 30 Hypercholesterolaemic rabbits display enhanced vascular expression of AT1 receptors that mediate increased activity of angiotensin II. 31 Furthermore, the effect of statins to reverse the elevated blood pressure response to angiotensin II infusion is accompanied by downregulated AT1 receptor density. 32, 33 Indeed, in apolipoprotein E (ApoE) null mice fed with a high-cholesterol diet, neither valsartan nor fluvastatin had any effect on blood pressure or cholesterol level; however, combined therapy with both drugs decreases plaque area and lipid deposition after 10 weeks. 34

Clinical Evidences of Cross-talk Between Statins and the Renin-angiotensin System

We reported additive beneficial effects of combined therapy with statins and RAS blockades on vascular and metabolic responses.
significantly increased plasma adiponectin levels and insulin sensitivity relative to baseline measurements (see Figure 3). These changes were significantly greater than those observed in the group treated with simvastatin alone. This study demonstrated that simvastatin combined with losartan improved endothelial function, reduced inflammatory markers and improved insulin sensitivity to a greater extent than monotherapy with either drug in hypertensive, hypercholesterolaemic patients.30,31 In our study, additive beneficial effects of combined therapy with statin and the ACE inhibitor ramipril were demonstrated in hypercholesterolaemic and patients with type 2 diabetes.32 Ramipril alone, simvastatin alone or combined therapy with ramipril and simvastatin treatment arms significantly improved flow-mediated dilator response to hyperaemia and reduced plasma levels of malondialdehyde (oxidative stress marker) relative to baseline measurements. However, these parameters were changed to a greater extent with combined therapy compared with either simvastatin or ramipril alone. Combined therapy or ramipril alone significantly increased plasma adiponectin levels and insulin sensitivity relative to baseline measurements compared with simvastatin or ramipril alone, combined therapy significantly reduced high-sensitivity CRP levels. Interestingly, in addition, combined therapy with ramipril and simvastatin had beneficial additive effects on tissue factor activity and prothrombin fragment 1+2 in patients with type 2 diabetes.33

These beneficial effects of combined statins with RAS blockades on endothelial function, inflammation and oxidative stress were confirmed by others. Twenty patients with type 2 diabetes took atorvastatin, irbesartan or both for one week. High-fat load and glucose alone produced a decrease in endothelial function and an increase in inflammation. These effects were more pronounced when high-fat load and glucose were combined. Short-term atorvastatin and irbesartan treatments significantly counterbalanced these phenomena, and their combination was more effective than either therapy alone.34 On-pump coronary artery bypass graft surgery is associated with an intense systemic inflammatory response that is almost completely prevented by early treatment with high doses of ACE inhibitors and statins.35 In a small, randomised, open-label study, combined therapy with rosuvastatin and telmisartan had favourable effects on homeostatic model assessment of insulin resistance (HOMA-IR), fasting serum insulin and high-sensitivity CRP (hs-CRP) compared with the rosuvastatin combined with irbesartan and rosuvastatin combined with olmesartan in Greek adults with impaired fasting glucose, mixed hyperlipidaemia and stage 1 hypertension. This study may suggest that AT1 receptor blocker (ARB), which has partial activator effect of peroxisome proliferator-activated receptor gamma (PPARgamma), would be more favourable on metabolic parameters when combined with statins.36

Clinical Perspectives of Cross-talk Between Statins and the Renin-angiotensin System

Impaired endothelial vasodilation is associated with increased cardiovascular event rates. Furthermore, endothelial dysfunction and increased vascular oxidative stress, inflammation and fibrinolysis status predict the risk of cardiovascular event rates in patients with coronary artery disease.37 Combined statins and RAS blockades improve endothelial function as reflected by improved flow-mediated dilation, improves fibrinolysis potential and reduced oxidant stress, inflammatory markers and insulin sensitivity. Recently, reciprocal relationships between endothelial dysfunction and insulin resistance have been proposed.1,39 In addition, there are some debates on unfavourable effects of statins on insulin sensitivity and development of diabetes.40–42 In terms of this important matter, combined therapy with statins and RAS blockades may improve insulin sensitivity and aid prevention of the development of new diabetes in patients at high risk of cardiovascular disease compared with statins alone.

Conclusion

In conclusion, there is a strong scientific rationale for recommending combination therapy, especially statins and RAS blockades to treat or prevent atherosclerosis and coronary heart disease.43–44 Combined therapy with statins and RAS blockades may be an important emerging concept in developing optimal treatment and prevention strategies for atherosclerosis, coronary heart disease and co-morbid metabolic disorders characterised by endothelial dysfunction and insulin resistance. In the future, randomised trials are needed to gain additional insight into the extent that combination therapy may be superior to monotherapy.

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