Statins and Renin-Angiotensin System Inhibitor Combination Treatment to Prevent Cardiovascular Disease

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Hypercholesterolemia and hypertension are common risk factors for cardiovascular disease (CVD). Updated guidelines emphasize target reductions of overall cardiovascular risks. Experimental studies have shown reciprocal relationships between insulin resistance (IR) and endothelial dysfunction. Hypercholesterolemia and hypertension have a synergistic deleterious effect on IR and endothelial dysfunction. Unregulated renin-angiotensin system (RAS) is important in the pathogenesis of atherosclerosis and hypertension. Various strategies with different classes of antihypertensive medications to reach target goals have failed to reduce residual CVD risk further. Of interest, treating moderate cholesterol elevations with low-dose statins in hypertensive patients reduced CVD risk by 35–40% further. Therefore, statins are important in reducing CVD risk. Unfortunately, statin therapy causes IR and increases the risk of type 2 diabetes mellitus. RAS inhibitors improve both endothelial dysfunction and IR. Further, cross-talk between hypercholesterolemia and RAS exists at multiple steps of IR and endothelial dysfunction. In this regard, combined therapy with statins and RAS inhibitors demonstrates additive/synergistic effects on endothelial dysfunction and IR in addition to lowering cholesterol levels and blood pressure when compared with either monotherapy in patients. This is mediated by both distinct and interrelated mechanisms. Therefore, combined therapy with statins and RAS inhibitors may be important in developing optimal management strategies in patients with hypertension, hypercholesterolemia, diabetes, metabolic syndrome, or obesity to prevent CVD. (Circ J 2014; 78: 281–287)

Key Words: Cardiovascular disease; Hypercholesterolemia; Hypertension; Renin-angiotensin system inhibitors; Statins

In the past, the goal of treating patients with hypertension or hypercholesterolemia was merely to control numerical factors such as blood pressure (BP) or serum cholesterol level alone; nowadays, it has changed. The updated guidelines target reductions in overall cardiovascular risk.\(^1\)\(^2\) Hypercholesterolemia and hypertension are both associated with endothelial dysfunction and insulin resistance (IR) and their coexistence is a vicious cycle associated with an increased incidence of cardiovascular events. Moreover, both risk factors are frequently prevail together.\(^3\)\(^4\) Indeed, more than 60% of hypertensive patients were consistently hypercholesterolemic in the United States National Health and Nutrition Examination Surveys 1988–2010.\(^5\) More importantly, the prevalence of dyslipidemia increased parallel to BP. In the prehypertensive range, prevalence was similar to that of the general population, approximately 26%; however, this prevalence doubles in the hypertensive population, reaching nearly 60%.\(^6\) Although it is not possible to provide a definite pathogenesis of hypertension-hypercholesterolemia/dyslipidemia clustering, it is gaining consensus that IR and endothelial dysfunction might play major roles.\(^7\)\(^8\)

From 1988–1994 to 2005–2010, control of concomitant hypertension and the low-density lipoprotein-cholesterol (LDL-C) level rose from 5.0% to 30.7%. By multivariable logistic regression, factors associated with concomitant hypertension, LDL-C, and non-high-density lipoprotein-cholesterol control were statin therapy (10.7) and antihypertensive (3.32) medications, and ≥2 healthcare visits/year (1.90), whereas age (0.77/10-year increase), black race (0.59), Hispanic ethnicity (0.62), cardiovascular disease (CVD) (0.44), and diabetes mel-
Recent published hypertension guidelines state that diuretics, β-blockers, calcium antagonists, angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin-receptor blockers (ARBs) are equally recommendable for the initiation and maintenance of antihypertensive treatment. However, it is also widely accepted that there are substantial differing effects on insulin sensitivity among the various classes of antihypertensive agents. The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT), a clinical outcome trial in 42,418 high-risk patients with hypertension, which compared 3 classes of antihypertensive agents as initial therapy of hypertension, showed an increased incidence of DM among diuretic-treated patients. Diuretic treatment resulted in 4–6 mg/dl higher fasting plasma glucose levels, causing 17% increased incidence of DM compared with other agents. Hypokalemia associated with thiazide diuretics is suggested to be the main mechanism of IR. β-blockers tend to increase body weight and cause IR, facilitating new-onset DM. It is still unclear why β-blockers impair insulin sensitivity; however, peripheral vasoconstriction by traditional β-blockers such as atenolol might limit glucose transportation to muscle, a major glucose-utilizing organ, thus causing decreased glucose metabolism. In contrast, new vasodilating β-blockers such as nebivolol and carvedilol are associated with more favorable effects on glucose and lipid profiles than non-vasodilating β-blockers.

In contrast, RAS inhibitors such as ACEIs and ARBs potentially improve insulin sensitivity in hypertensive patients. The RAS also has multiple effects in the central nervous system, skeletal muscle, liver, and adipose tissue that may interfere with insulin action. Thus, RAS dysregulation may contribute to the evolution of IR, and conversely, RAS blockade may potentially help prevent new-onset DM. RAS blockade may have direct effects that augment insulin-stimulated glu-
During IR, the cardiovascular system is sensitized to the adverse trophic effects of RAS, which is evidenced by the frequent occurrence of diffuse vascular disease and left ventricular hypertrophy in diabetic patients, even when the lipid and BP levels are normal. High insulin levels stimulate the adipose tissue where they may have unfavorable pleiotropic effects including secondary actions on the cardiovascular system. In vessels, angiotensin II promotes superoxide anion generation and endothelial dysfunction. Angiotensin II activates nuclear transcription factor (NF-kB) induced by oxidative stress, mediated by the AT1 receptor. In our previous study, candesartan significantly improved flow-mediated vasodilation and reduced plasma levels of oxidant stress, and markers of inflammation, hemostasis, independent of BP reduction. This finding showed that ARBs reverse endothelial dysfunction and reduce oxidant stress and inflammatory cytokines, suggesting that ARBs have antiatherogenic effects in hypertensive patients.

**Effects of Statin Therapy on IR**

3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors (statins) are effective in lowering cholesterol and decreasing cardiovascular morbidity and mortality. Statins have pleiotropic effects that go beyond lowering the cholesterol level per se. For example, statins improve endothelial-dependent vasodilation, increase the bioavailability of nitric oxide (NO), and reduce the levels of endothelin-1 (a potent vasoconstrictor). Moreover, statins reverse the elevated BP response to angiotensin II infusion, accompanied by increased AT1 receptor density.

Interestingly, high-dose statins have an off-target effect; for example, worsening insulin sensitivity that may be uncomfortable when using statins to reduce overall morbidity and mortality. Indeed, lipophilic and hydrophilic statins have markedly different effects on IR in many studies. Lipophilic statins, particularly at high doses, cause unfavorable effects, reducing insulin secretion and aggravating IR. Lipophilic statins inhibit synthesis of isoprenoid and suppress ubiquinone (coenzyme Q10) biosynthesis, which might delay ATP synthesis by pancreatic β-cells, leading to impaired insulin secretion. It is also possible that lipophilic statins are taken up by the brain and fat tissue where they may have unfavorable pleiotropic effects including secondary actions on the regulation of insulin secretion and exacerbation of IR. In contrast, a hydrophilic statin, pravastatin, improves insulin sensitivity and increases circulating adiponectin levels in humans, which may have beneficial metabolic effects as well as reduce atherogenesis.

We reported that high-dose simvastatin reduced adiponectin

![Figure 2. Differential effect of lipophilic and hydrophilic statins on insulin sensitivity. Lipophilic simvastatin significantly decreased plasma adiponectin levels and insulin sensitivity when compared with baseline. In contrast, pravastatin significantly increased plasma adiponectin levels and insulin sensitivity when compared with baseline. Moreover, these effects of pravastatin were significant when compared with placebo and simvastatin. Standard error of the mean is identified by the bars. Pl, placebo; P40, pravastatin 40mg; QUICKI, Quantitative Insulin-Sensitivity Check Index; S20, simvastatin 20mg. (Reproduced with permission from Koh et al. 49)](image-url)
Our group also reported that hypercholesterolemic patients receiving high-dose atorvastatin (80 mg) had a higher incidence of IR with higher fasting insulin and glycated hemoglobin HbA1c levels when compared with those taking the low dose (10 mg) or placebo, suggesting that high-dose statin therapy may have greater adverse effects on glucose homeostasis than low-dose therapy (Figure 3). 

In a comparison study of simvastatin and pravastatin, simvastatin (20 mg) significantly increased fasting insulin levels and decreased plasma adiponectin levels and insulin sensitivity, whereas pravastatin (40 mg) treatment did not significantly change insulin levels but significantly increased plasma adiponectin levels and insulin sensitivity at equivalent lipid-lowering doses (Figure 2). 

Figure 3. Dose-dependent adverse effects of lipophilic statins in insulin sensitivity. Hypercholesterolemic patients receiving the higher dose of atorvastatin developed higher fasting insulin levels and incidence of IR when compared with patients receiving the lower dose or placebo. Standard error of the mean is identified by the bars. QUICKI, Quantitative Insulin-Sensitivity Check Index. (Reproduced with permission from Koh et al. 44)

Figure 4. Synergistic effect of statins and renin-angiotensin system (RAS) inhibitors on insulin sensitivity. In 48 hypercholesterolemic patients, both pravastatin 40 mg and valsartan 160 mg increased plasma adiponectin levels, reduced fasting insulin levels, and increased insulin sensitivity relative to baseline measurements. When pravastatin was combined with valsartan, the response increased in an additive manner when compared with monotherapy alone. Median values (A,B) or mean with SEM (C) are provided. QUICKI, Quantitative Insulin-Sensitivity Check Index. (Reproduced with permission from Koh et al. 60)
Rosuvastatin is less hydrophilic than pravastatin but increased the incidence of type 2 DM in a large clinical trial.\(^{45}\) We recently reported that hypercholesterolemic patients receiving rosuvastatin 10 mg had worsened insulin sensitivity and glucose control during the 8 weeks when compared with placebo.\(^{46}\)

**Statin Combined With RAS Inhibitor Therapy to Maximize Cardiovascular Protection**

Endothelial dysfunction and IR play crucial roles in the pathogenesis of atherosclerosis. A positive correlation between IR and endothelial function was also reported in obese hypertensive subjects.\(^{47}\) Importantly, elevated levels of free fatty acids associated with IR, obesity, DM, and the metabolic syndrome cause endothelial dysfunction by activating innate immune inflammatory pathways upstream of NF-κB.\(^{48}\) Thus, inflammation and oxidative stress contribute to endothelial dysfunction and IR, while endothelial dysfunction and IR promote oxidative stress and inflammation.\(^{4,49,50}\) There is a reciprocal relationship between IR and endothelial dysfunction. In this respect, reversing IR is another important part of hypertension treatment, together with BP control.

Of note, statins and RAS inhibitors have the potential to exert synergistic effects on both endothelial function and insulin sensitivity. Statins improve endothelial function via stimulation of endothelial NO synthase (eNOS) activity and mediate antioxidant effects that result in enhanced NO bioactivity.\(^{43,51,52}\) Hyperglycemia impairs endothelial function whereas statins reversed endothelial dysfunction in both in vitro and in vivo studies using a type 2 DM animal model, OLETF rats.\(^{53}\) In addition, hypercholesterolemic rabbits display enhanced vascular expression of AT1 receptors, which mediate increased activity of angiotensin II, thus increasing BP.\(^{54}\) Statins reverse
the BP-elevating response to angiotensin II infusion by decreasing AT1 receptor density. Conversely, RAS inhibitors also improve endothelial function through potentiating shear-stress induced NO production via modulation of eNOS phosphorylation.

Indeed, in apolipoprotein-E null mice fed with a high-cholesterol diet, neither valsartan nor fluvastatin had any effect on the BP or cholesterol level. However, combined therapy with both drugs significantly decreased plaque area and lipid deposition after 10 weeks, compared with either monotherapy. We reported vascular and metabolic responses to treatment with statin and RAS inhibitor alone or in combination in hypertensive, hypercholesterolemic patients: simvastatin combined with losartan improved endothelial function and insulin sensitivity in these subjects. In another study, statin combined with the ACEI, ramipril, had beneficial additive effects on endothelial function and insulin sensitivity in patients with type 2 DM. In type 2 DM patients, atorvastatin combined with irbesartan treatment showed additive effects over either monotherapy. Recently, we observed that pravastatin combined with valsartan therapy increased plasma adiponectin level, lowered the fasting insulin level, and improved insulin sensitivity in an additive manner when compared with monotherapy alone in a hypertensive population (Figure 4).

Conclusions

Hypercholesterolemia and hypertension share a common pathophysiology such as endothelial dysfunction and IR, and both are the most common risk factors of CVD. Indeed, more than 60% of hypertensive patients are hypercholesterolemic. Various strategies to reduce residual CVD risk in hypertensive patients included lowering goals for BP and other end points of antihypertensive medications, but the results have not greatly changed. However, treating moderate cholesterol elevations with low-dose statins reduces CVD by 35–40%. Unfortunately, statin therapy causes IR and increases the risk of type 2 DM. On the other hand, RAS inhibitors improve both endothelial dysfunction and IR in addition to BP lowering. Of interest, cross-talk between hypercholesterolemia and RAS exists at multiple steps of IR and endothelial dysfunction. Combined therapy with statins and RAS inhibitors demonstrates synergistic effects on endothelial function and insulin sensitivity in addition to lowering cholesterol levels and BP when compared with either monotherapy in patients with cardiovascular risk factors. This is mediated by both distinct and interrelated mechanisms (Figure 5). Therefore, there is a strong scientific rationale for recommending combination therapy to treat or prevent atherosclerosis and coronary artery disease.

In summary, combined therapy with statins and RAS inhibitors may be important in the development of optimal management strategies to prevent CVD in patients with hypertension, hypercholesterolemia, DM, metabolic syndrome, or obesity.

References


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