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The importance of considering alternative or combination strategies for lowering LDL-C

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Aggressive intervention to lower low-density lipoprotein cholesterol (LDL-C) with statin therapy significantly reduces cardiovascular risk [1]. Target levels of LDL-C levels between 50 to 70 mg/dl and even more aggressive treatment of hypercholesterolemia in high-risk patients has been suggested [2]. While beneficial effects of lowering LDL-C have been substantiated in multiple clinical trials, there remains uncertainty regarding optimal LDL-C targets. Moreover, understanding risks of adverse non-cardiovascular events associated with lowering LDL-C levels using statin therapy alone is of great clinical importance as physicians and patients balance risk versus benefit.

The safety of statins at high dosages, particularly with respect to cancer, is controversial [3]. The Simvastatin and Ezetimibe in Aortic Stenosis (SEAS) study reports fewer patients with ischemic cardiovascular events but higher incidence of cancer in the simvastatin-ezetimibe treatment group (mean age 67.7 years, mean serum LDL-C decreases from 140 to 53 mg/dl after 5 years) [4]. In the Treating to New Targets study, a trend towards increased cancer deaths (85 cases vs. 75 cases, not statistically significant) was observed in the intensive atorvastatin arm (80 mg versus 10 mg) [5]. However, overall cancer incidence was not reported in this study. These recent reports are consistent with epidemiological studies that find associations between low cholesterol levels and higher incidence of cancer [6]. Increase in cancer deaths in epidemiologic studies may counterbalance lower cardiac mortality resulting from lower cholesterol. Thus, there tends to be a neutral effect of high dose statins on overall mortality across cholesterol levels [7,8]. In meta-analyses of randomized statin trials, statin use in itself is not associated with an increased risk of cancer when compared with placebo [9]. However, a significant inverse association exists between cancer incidence and lower LDL-C levels. No such association is present with percent LDL-C reduction or absolute LDL-C reduction [3]. It remains possible that increased cancer deaths may offset lower cardiac mortality associated with reduced cholesterol in some patients.

Alsheikh-Ali et al. [10] report that the LDL-C-lowering effect of statins is not associated with an increased risk of cancer despite an inverse association between on-treatment LDL-C levels and incident cancer. They also report that in the statin treatment arms, there is a significant relationship between incident cancer, age, and history of hypertension. When we examine the incidence of cancer and its relationship with statin treatment for LDL-C levels, age, and hypertension from clinical trials using pravastatin (e.g., PROSPER, CARE, LIPID, WOSCOP, and MEGA studies), pravastatin treatment for LDL-C levels and age may be important factors

contributing to increased risk of cancer. When compared with the PROSPER study (post-treatment LDL-C levels 107 mg/dl and mean age 75 years), the MEGA study reports that relatively low doses of pravastatin (post-treatment LDL-C levels 128 mg/dl) is associated with less incidence of cancer and comparable cardiovascular events in patients with mean age 58 years (Table 1). The Jupiter study reports no significant differences in newly diagnosed cancer, but a statistically significant decrease in cancer deaths in the rosuvastatin arm versus the placebo arm (this was stopped after a median follow-up of 1.9 years) [11]. 1.9 years may not be long enough to make valid conclusions regarding changes in the incidence of cancer.

Due to pleiotropic effects of statins, achieving LDL-C targets using statins alone (especially at high dose) may not be as beneficial as attaining similar LDL-C levels by alternative means. In this regard, one study compared effects of aggressive (simvastatin 80 mg) and conventional (simvastatin 20 mg) lipid lowering on early human atherosclerotic lesions using serial noninvasive magnetic resonance imaging. Although these statin doses reduced LDL-C by 36% (conventional, 20 mg) and 46% (aggressive, 80 mg), both groups reached similar absolute values after treatment. A significant reduction in atherosclerotic vessel wall area was already observed by 12 months. No difference in vascular effects was detected between the different randomized doses. Post-hoc analysis shows that patients reaching mean on-treatment LDL-C ≤ 100 mg/dl had larger decreases in plaque size [12]. Thus, changes in vessel wall parameters are determined primarily by LDL-C reduction rather than the dose of statin used. In 1255 subjects with type 2 diabetes mellitus receiving maintenance hemodialysis who were randomly assigned to receive 20 mg of atorvastatin per day or matching placebo, the median level of LDL-C was reduced by 42% among patients receiving atorvastatin. During a median follow-up period of four years, atorvastatin had no significant effect on the individual components of the primary end point, except that the relative risk of fatal stroke among those receiving atorvastatin was 2.03 (95% confidence interval, 1.05 to 3.93; $P=0.04$). Atorvastatin reduced the rate of all cardiac events combined (relative risk, 0.82; 95% confidence interval, 0.68 to 0.99; $P=0.03$, nominally significant) but not all cerebrovascular events combined (relative risk, 1.12; 95% confidence interval, 0.81 to 1.55; $P=0.49$) or total mortality (relative risk, 0.93; 95% confidence interval, 0.79 to 1.08; $P=0.33$) [13]. The high-density lipoprotein-cholesterol (HDL-C) level in patients receiving statins was predictive of major cardiovascular events across the TNT study cohort, both when HDL-C was considered as a continuous variable and when subjects were stratified according to quintiles of HDL-C level. When the analysis was stratified according to LDL-C level in patients receiving statins, the relationship between HDL-C level and major cardiovascular events was of borderline significance ($P=0.05$). Even among study subjects with LDL-C levels below 70 mg/dl, those in the highest quintile of HDL-cholesterol level were at less risk for major cardiovascular events than those in the lowest quintile ($P=0.03$) [14]. Taken together, these studies indicate that aggressive statin therapy carries some risks that need to be considered when deciding on the optimal therapeutic strategy for treatment of hypercholesterolemia in individual patients.

Combining low dose statin treatment with other therapies to achieve the same target LDL-C level may allow for beneficial cardiovascular effects of low LDL-C while minimizing adverse outcomes from high dose statin treatment. Thus, it may be prudent to reduce LDL-C levels to ~ 70 mg/dl with statins alone only in patients with very high cardiovascular risk. In light of pleiotropic effects of statins, combination therapy may be an important consideration for a majority of patients [15-19]. Overall mortality rates are determined by more than a single biomarker. In addition, the mechanisms by which a biomarker is altered may contribute importantly to the clinical outcome. Hypercholesterolemia and hypertension have synergistic deleterious effects on endothelial dysfunction and increased incidence of cardiac events [20]. In atherosclerotic cardiovascular diseases, reciprocal relationships between insulin resistance and endothelial dysfunction exist (Fig. 1) [21]. There is also cross-talk between hyperlipidemia and renin-angiotensin-aldosterone system at multiple steps [18,19]. Thus, combination therapy

with statins and renin-angiotensin-aldosterone system blockers or peroxisome proliferator-activated receptors (PPARs) may be more beneficial than monotherapy. Indeed, we demonstrate that ramipril, losartan, or fenofibrate combined with statins significantly reduces blood pressure, improves the lipoprotein profile and endothelial function and reduces inflammatory markers and insulin resistance to a greater extent than monotherapy in patients with type 2 diabetes [16], hypercholesterolemic and hypertension [15] (Fig. 2), or combined hyperlipidemia [17]. These superior benefits of combination therapy are likely mediated by both distinct and interrelated mechanisms that simultaneously target blood pressure, atherosclerosis, and coronary heart disease (Fig. 3) [22,23].

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Fig. 1.

A. Parallel phosphatidylinositol 3-kinase-dependent insulin signaling pathways in metabolic and vascular tissues synergistically couples metabolic and vascular physiology under healthy conditions. B. Parallel impairment in insulin signaling pathways under pathological conditions contributes to synergistic coupling of insulin resistance and endothelial dysfunction.

Reproduced from Kim et al. [21].

Fig. 2.

A. Percent change in malondialdehyde levels from respective pretreatment values after treatment with simvastatin alone, combined therapy, and losartan alone. Percent change in flow-mediated dilation (FMD) from respective pretreatment values after treatment with simvastatin alone, combined therapy, and losartan alone. The combined therapy with simvastatin and losartan significantly reduced malondialdehyde levels and improved FMD when compared with simvastatin and losartan alone. B. Percent change in adiponectin levels from respective pretreatment values after treatment with simvastatin alone, combined therapy, and losartan alone. Percent change in Quantitative Insulin-Sensitivity Check Index (QUICKI) from respective pretreatment values after treatment with simvastatin alone, combined therapy,

and losartan alone. The combined therapy with simvastatin and losartan significantly increased adiponectin levels and QUICKI when compared with simvastatin and losartan alone. SEM is identified by bars. Reproduced with permission from Dr. Koh [15].

Fig. 3.

Many stimuli initiate transcription of genes in endothelium that encode protein mediators of inflammation and hemostasis. Renin-angiotensin-aldosterone system (RAAS) is the most important in the pathogenesis of atherosclerosis. Angiotensin II (Ang II) binds to angiotensin II type I receptor (AT1R) and produce oxygen free radicals by using enzymes. Oxygen free radicals dissociate inhibitory factor, IκB and thus activate NF-κB. Activated NF-κB stimulates the expression of proinflammatory genes in the nucleus and the production of proinflammatory proteins such as chemokines and cytokines. Recent experimental studies have shown the reciprocal relationships between insulin resistance and endothelial dysfunction. Experimental studies have shown a cross-talk between hyperlipidemia and RAAS at multiple steps. Combined therapy with statins, peroxisome proliferators-activated receptors (PPARs), and RAAS blockades show additive beneficial effects on endothelial dysfunction and insulin resistance when compared with monotherapies in patients with cardiovascular risk factors by both distinct and interrelated mechanisms. Adapted from Dr. Koh [18,22,23].

Table 1

Incidence of cancer and its relationship with statin treatment for LDL-C levels, age, and hypertension from clinical trials using pravastatin.

	Age (yrs)	On-Tx LDL-C (mg/dl)	HT (%)	Incident cancer
				Statin vs placebo
PROSPER	75	107	62	245 vs 199
CARE	59	97	42	172 vs 161
LIPID	62	113	41	379 vs 399
MEGA	58	128	42	119 vs 126
WOSCOP	55	142	16	116 vs 106

On-Tx LDL-C = on treatment low-density lipoprotein cholesterol, HT=hypertension

PROSPER=Prospective Study of Pravastatin in the Elderly at Risk;

CARE=Cholesterol and Recurrent Events trial;

LIPID=Long-Term Intervention with Pravastatin in Ischemic Disease study;

MEGA=Management of Elevated Cholesterol in the Primary Prevention Group of Adult Japanese study;

WOSCOPS=West of Scotland Coronary Prevention Study.