Antioxidant Effects of Statins in the Management of Cardiometabolic Disorders

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Redox systems are key players in vascular health. A shift in redox homeostasis—that results in an imbalance between reactive oxygen species (ROS) generation and endogenous antioxidant defenses has the potential to create a state of oxidative stress that subsequently plays a role in the pathogenesis of a number of diseases, including those of the cardiovascular and metabolic system. Statins, which are primarily used to reduce the concentration of low-density lipoprotein cholesterol, have also been shown to reduce oxidative stress by modulating redox systems.

Studies conducted both in vitro and in vivo support the role of oxidative stress in the development of atherosclerosis and cardiovascular diseases. Oxidative stress may also be responsible for various diabetic complications and the development of fatty liver. Statins reduce oxidative stress by blocking the generation of ROS and reducing the NAD⁺/NADH ratio. These drugs also have effects on nitric oxide synthase, lipid peroxidation and the adiponectin levels.

It is possible that the antioxidant properties of statins contribute to their protective cardiovascular effects, independent of the lipid-lowering actions of these agents. However, possible adverse effects of statins on glucose homeostasis may be related to the redox system. Therefore, studies investigating the modulation of redox signaling by statins are warranted.


Key words: Redox, Statin, Antioxidant, Reactive oxygen species, Cardiometabolic disorders

Abbreviations: HMG-CoA: 3-hydroxy-3-methylglutaryl CoA, ROS: Reactive oxygen species, LDL: Low-density lipoprotein, TNFα: Tumor necrosis factor-α, IL6: Interleukin-6, PPARγ: Peroxisome proliferators-activated receptors-γ, SOD1: Superoxide dismutase 1, VLCFAs and LCFAs: Very long and long chain fatty acids, NAFLD: Non-alcoholic fatty liver disease, NASH: Non-alcoholic steatohepatitis, IL8: Interleukin-8, TGFβ: Transforming growth factor-β, PKC: Protein kinase C, NAD+: Nicotine adenine dinucleotide, DMSO: Dimethyl sulfoxide, NO: Nitric oxide, AT1: Angiotensin II type I, NOS: Nitric oxide synthase, CAD: Coronary artery disease, HDL: High-density lipoprotein, RAAS: Renin-angiotensin-aldosterone system, Ang II: Angiotensin II, QUICKI: Quantitative Insulin-Sensitivity Check Index

Introduction

Statins, 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors, are widely prescribed in clinical practice to reduce the plasma levels of low-density lipoprotein (LDL) cholesterol. Currently, more than 25 million individuals worldwide take statins. Treatment with statins has been shown to reduce cardiovascular morbidity and mortality in many landmark clinical trials, and a number of studies suggest that statins have beneficial effects on the cardiovascular system beyond lowering LDL-cholesterol. The 2013 American Heart Association/
Role of the Redox System in the Genesis of Metabolic and Cardiovascular Disorders

Redox signaling is an important process in a variety of cellular activities, such as cell proliferation, migration, differentiation and apoptosis\(^\text{16-18}\). Redox injury, as a pathological mechanism, is involved in a wide range of pathophysiological processes, including senescence, inflammation, hypoxia and ischemia/reperfusion\(^\text{19, 20}\), all of which may contribute to the progression of various diseases, from cardiovascular disorders, such as hypertension\(^\text{21}\) and atherosclerosis\(^\text{22}\), to metabolic conditions, such as fatty liver\(^\text{23}\) and type 2 diabetes mellitus (T2DM)\(^\text{24}\). A schematic representation of the interplay between the redox system, inflammatory processes and development of atherosclerosis is provided in Fig. 1.

Cardiovascular Disease

Lipid Oxidation and Oxidized LDL

LDL oxidation is a key player in the initiation of these drugs in treating cardiovascular disorders as well as other chronic conditions associated with oxidative stress. The possible adverse effects of statins on glucose homeostasis, which may be related to the redox system, are also discussed.
and progression of atherosclerosis [14]. LDL is oxidized by ROS released from circulating and vascular wall cells [25, 26]. Biochemically, LDL oxidation is the consequence of free radical driven chain reactions in which polyunsaturated fatty acids are converted to lipid peroxides that subsequently generate a range of biologically active aldehydes [27].

Oxidatively modified LDL, or oxidized LDL, is involved in the early development of atherosclerotic lesions [14]. Several in vitro studies have shown that lipid-laden foam cells are formed after macrophages take up oxidized LDL [10, 28, 29]. In addition, the presence of lipid-laden foam cells is a typical feature of vulnerable atherosclerotic lesions. Therefore, the oxidative modification of LDL plays a role in the development of atherosclerotic lesions via the formation of foam cells [13]. Recent evidence indicates that modified apolipoprotein B derived from oxidized LDL accumulates in foam cells [29]. Furthermore, macrophage-derived foam cells contain many lipid droplets in the cytoplasm, and the levels of oxidized LDL are increased in patients with a history of acute myocardial infarction and carotid artery atherosclerosis [28, 30-32].

Although the role of oxidized LDL in vivo is not completely understood, it has been suggested that measuring the level of oxidized LDL in the plasma may be helpful for predicting the incidence of cardiovascular events [28, 30]. Moreover, the presence of oxidized LDL in the LDL fraction of human plasma has been demonstrated using ELISA assays [30, 32]. The accumulation of oxidized LDL in atherosclerotic lesions has also been documented based on the findings of immunohistochemical staining using monoclonal antibodies [33].

**Relationship between Inflammation and Oxidative Stress in the Setting of CVD**

Inflammation is a complex process that impacts the onset and progression of atherosclerosis and CVD in many different ways [34, 35]. Inflammatory markers shown to be elevated in patients with CVD include the levels of C-reactive protein, interleukin-8 (IL8), monocyte chemoattractant protein-1 (MCP1) and tumor necrosis factor-α (TNFα), all of which play a crucial role in recruiting neutrophils, T lymphocytes and monocytes to the vascular wall [36, 37]. In addition, increased CD40-CD40 ligand interactions result in a prothrombotic state [38], while increased matrix metalloproteinases lead to plaque rupture [39].

Many inflammatory processes are involved in the production and actions of ROS by NAD(P)H oxidase in the vascular wall cell [9]. For example, nuclear factor (NF)-κB, a transcription factor that plays a key role in the expression of proinflammatory cytokines, is positively regulated by ROS [40]. Consistent with this observation, dimethyl sulfoxide (DMSO), a scavenger of ROS, inhibits the release of proinflammatory cytokines [41], whereas ROS contribute to the formation of oxidized LDL, which in turns leads to the deposition of foam cells in atherosclerotic plaques [10]. Therefore, oxidative stress and inflammation are important causative factors for atherosclerotic vascular diseases, particularly under conditions of diabetes [42].

**Diabetes Mellitus and its Complications**

Oxidative stress associated with lipotoxicity has been known to contribute to the development of T2DM. Mitochondrial dysfunction and lipid homeostasis disruption may also play a role in the onset of insulin resistance [43], while functional impairments in mitochondria induce adipocyte dysfunction with a subsequent increase in the circulating levels of free fatty acids (FFAs) and their abnormal deposition in pancreatic β-cells, thus resulting in lipotoxicity and mitochondrial and pancreatic β-cell dysfunction [44, 45].

Several mechanisms have been proposed for the development of diabetic complications (Fig. 2), including: (1) an increase in the activity of the polyol pathway, (2) an increase in the activity of the hexosamine pathway, (3) an increase in the formation of advanced glycation end-products, (4) activation of the protein kinase C (PKC) pathway and (5) an increase in the activity of proinflammatory pathways [46-49]. Of note, the overactivation of these pathways is caused by the hyperglycemia-induced overproduction of superoxide anions by the mitochondrial electron transport chain. Since the activity of glyceraldehyde phosphate dehydrogenase (GAPDH), a key glycolytic enzyme, is downregulated by superoxide anions, a reduction in the speed of glycolysis leads to an increase in ROS production, thus augmenting a vicious negative feedback cycle [50].

In this context, an imbalance of nicotinamide adenine dinucleotide (NAD+) and NADH, its reduced form, is a key contributor to target organ damage in patients with diabetes mellitus. NAD+ is a coenzyme found in all living cells. NADH is abundant in the cytosol and is an important reducing agent in many enzymatic reactions [51, 52]. NAD+/NADH is transported by carriers such as the malate-aspartate shuttle [53]. The balance between NAD+ and NADH is important for the regulation of the redox system in cells [54, and NADP+/NADPH regulates the activities of enzymes involved in the sirtuin 1, pyruvate dehydrogenase and GAPDH pathways, all of which play a role in the onset of diabetes and its complications [45, 54, 56]. Therefore, an imbalance in the redox system contributes to
the development of diabetes mellitus and its complications.

**Obesity and Metabolic Syndrome: Relationships between Insulin Resistance, Oxidative Stress and Inflammation Leading to CVD**

Systemic oxidative stress is associated with abdominal obesity and insulin resistance. Along with oxidative stress, chronic low-intensity inflammation is clinically evident in obese and insulin-resistant subjects, manifesting as increased levels of inflammatory biomarkers, such as C-reactive protein, TNFα, IL6 and fibrinogen.

Metabolic syndrome, defined as the clustering of obesity, dyslipidemia, hypertension and insulin resistance, is a well-known risk factor for the development of T2DM and CVD. Patients with metabolic syndrome frequently have a lipid profile characterized by high triglyceride and low HDL-cholesterol levels with an LDL fraction that is usually not increased in concentration but which consists of small, dense particles that are more susceptible to oxidation. This pattern is highly atherogenic. According to the Coronary Artery Risk Development in Young Adults study, a high concentration of oxidized LDL is associated with an increased incidence of abdominal obesity, hyperglycemia, hypertriglyceridemia and metabolic syndrome. In a study investigating the association between insulin resistance and lipid peroxidation, patients with metabolic syndrome and/or T2DM were found to have increased levels of oxidation products of linoleic acid and malondialdehyde. Oxidized LDL activates smooth muscle cells and macrophages to produce gelatinase, which leads to the development of vulnerable plaques. In an experimental study, preadipocytes exposed to oxidized LDL displayed a high rate of proliferation, low level of apoptosis and increased pre-adipocyte factor-1 mRNA expression. These findings suggest that oxidized LDL is a modulator of adipose tissue differentiation and provides a possible link between obesity and its clinical complications.

An increased level of oxidized LDL may be due in part to an impaired HDL-associated antioxidant defense. HDL is known to prevent the formation of oxidized LDL by eliminating seeding molecules from...
The paraoxonase-1 (PON1) activity associated with HDL has the ability to protect LDL against oxidative modification, and a low level of PON1 is a predictive factor of multivessel involvement of the coronary arteries in patients with hyperglycemia. Furthermore, the level of oxidized LDL correlates positively with the expression of toll-like receptor 2 and interferon regulatory factor 1, suggesting a relationship between oxidative stress and inflammation in the process of atherosclerotic plaque formation.

**Fatty Liver**

Non-alcoholic fatty liver disease (NAFLD) is characterized by the accumulation of intrahepatic triglycerides unrelated to alcohol consumption. NAFLD is often considered to be the hepatic manifestation of insulin resistance. The number of individuals with NAFLD in Western countries is increasing, and the condition has become the most common cause of chronic liver disease. In the large cohorts, subjects with NAFLD have been found to have an increased risk of developing metabolic syndrome and T2DM. NAFLD includes a spectrum of disturbances encompassing various degrees of liver damage, ranging from simple lipid accumulation to non-alcoholic steatohepatitis (NASH), which is characterized by the presence of hepatocellular inflammation in association with fibrosis. NAFLD may progress to NASH and is a risk factor for the development of CVD as well as hepatocellular carcinoma.

Oxidative stress plays a major role in the onset of NAFLD. Altered reduction/oxidation reactions generate ROS, thus leading to damage of hepatocytes. Very long and long chain fatty acids (VLCFAs and LCFAs) are oxidized by peroxisomes and metabolized as a result of microsomal oxidation. After the VLCFAs and LCFAs chains are shortened by peroxisomal and microsomal oxidation, they are oxidized in the mitochondrial oxidation system. Under conditions of insulin resistance, an increased amount of FFAs is released from adipose tissue and taken up by the liver. This overflow of FFAs increases ROS production as well as decreases the activity of antioxidant systems, thereby inducing oxidative stress. Mitochondria are responsible for oxidative phosphorylation and fatty acid beta-oxidation. These organelles are, in turn, the major source of ROS and are susceptible to oxidative damage. The excessive generation of ROS itself may be considered a direct effect of mitochondrial dysfunction, which acts synergistically with inflammation in the generation of ROS, subsequently encouraging the progression from simple steatosis to NASH.

ROS also induce the secretion of cytokines, such as TNFα, IL8 and transforming growth factor-β (TGFβ), all of which play a role in the development of steatohepatitis and fibrosis.
Triglycerides derived from circulating FFAs accumulate in the liver, which may lead to the onset of inflammation mediated by CD36. CD36 and its receptor play an important role in facilitating fatty acid uptake, which precedes the secretion and storage of triglycerides. CD36 is also involved in the inflammatory response in both adipocytes and macrophages associated with complications of diet-induced obesity. Furthermore, insulin resistance plays an important role in the relationship between triglyceride accumulation and inflammation, as triglyceride accumulation in the liver aggravates hepatic insulin resistance, which subsequently induces low-grade inflammation. This series of events ultimately contributes to the development of steatohepatitis (Fig. 3).

Taken together, the pathogenesis of NAFLD is not yet fully understood; however, accumulated data suggest that oxidative stress and an altered redox balance play critical roles in the onset of NAFLD and its progression from steatosis to steatohepatitis.

**Role of Statins in the Redox System from a Cardiovascular and Metabolic Perspective**

Statin therapy decreases cholesterol synthesis by inhibiting 3-hydroxy-3-methylglutaryl CoA reductase, which subsequently increases the activity of the LDL receptor and decreases the concentration of LDL-cholesterol in the plasma. In many large trials, treatment with statins has been shown to decrease cardiovascular morbidity and mortality by reducing LDL. Statins improve NO bioactivity by inhibiting the actions of NF-κB and decreasing inflammatory protein production, both of which further contribute to preventing the onset and progression of atherosclerosis.

**Role of the Antioxidant and Anti-Inflammatory Effects of Statins in Treating CVD**

A number of studies have demonstrated that statins directly inhibit LDL-cholesterol oxidation. In addition, LDL-cholesterol isolated from patients...
treated with simvastatin has been found to be protective against LDL oxidation\textsuperscript{94}, while fluvastatin inhibits LDL oxidation\textsuperscript{15} and preferentially scavenges radicals directly\textsuperscript{96}. Interestingly, a direct comparison between fluvastatin and pravastatin found that fluvastatin exhibits much greater inhibition of LDL oxidation than pravastatin\textsuperscript{96}. This reduction in lipid peroxidation may contribute to the ability of statins to prevent or reduce atherosclerosis\textsuperscript{97}.

Nitric oxide (NO), the smallest signaling molecule, is produced by NO synthase and controls vascular tone\textsuperscript{98}. The upregulation of NO formation without increases in superoxide production induced by statin treatment contributes to the inhibition of lipid peroxidation. In addition to its role as a potent endogenous vasodilator\textsuperscript{99}, NO possesses anti-inflammatory and antioxidant activities\textsuperscript{100} by inhibiting the release of proinflammatory cytokines\textsuperscript{101} and the expression of endothelial cell adhesion molecules\textsuperscript{102}. NO is catalyzed by a family of NOS enzymes\textsuperscript{103}, and statins have been shown in both human studies and animal models to upregulate the NOS-3 expression\textsuperscript{104} in a process that improves the endothelial function\textsuperscript{105, 106}. In studies designed to determine the mechanism of eNOS upregulation induced by statins, mevastatin has been shown to significantly increase the levels of both eNOS mRNA and proteins in human endothelial cells\textsuperscript{107}. In addition, simvastatin and atorvastatin enhance the eNOS activity by activating the phosphatidylinositol 3-kinase/Akt pathway and decreasing cavelon abundance, respectively\textsuperscript{108, 109}, and atorvastatin has been reported to reduce the infarct size by increasing the activity of iNOS\textsuperscript{110}. Hence, statins have the potential to enhance NO bioavailability in the vasculature by decreasing superoxide production and subsequent NO breakdown as well as upregulating NOS.

In addition, atorvastatin has been reported to inhibit platelet-mediated LDL oxidation and isoprostane formation\textsuperscript{111}. A recent study also demonstrated that atorvastatin therapy acutely reduces oxidative stress by inhibiting Nox2 in platelets\textsuperscript{112}, while pitavastatin has been reported to mitigate oxidative stress and reduce elevated levels of ROS and NADPH oxidase in high-risk animal models\textsuperscript{113, 114}. Furthermore, statins decrease the mRNA expression of NADPH oxidase subunits\textsuperscript{115}. These data suggest that statins exert antioxidant effects by modulating the NADPH-oxidase enzyme activity.

Statins are also involved in the isoprenylation pathway. The cardioprotective effects of statins may be related to the reduced synthesis of mevalonate, the immediate product of HMG-CoA reductase, rather than that of cholesterol itself. Moreover, statins inhibit the translocation of Rac-1, which is required for the production of NADPH oxidase, to the membrane\textsuperscript{11, 115}. These effects of statins serve to reduce the oxidative stress burden on the vasculature.

Atorvastatin and lovastatin increase the production of catalase in the liver and aortic vascular smooth muscle cells\textsuperscript{11, 116}. Rosuvastatin is known to have antioxidant properties due to its upregulation of glutathione synthesis\textsuperscript{117}. In addition, one study showed that pitavastatin directly inhibits the formation of ROS in endothelial cells\textsuperscript{118}. Therefore, individual statins exert distinct antioxidant effects via diverse mechanisms and/or their actions in various cell systems.

Statins have a number of anti-inflammatory effects\textsuperscript{5, 119}. For example, they reduce the level of C-reactive protein, a marker of inflammation and an independent predictor of CVD\textsuperscript{4, 120}. Meanwhile, atorvastatin inhibits both proinflammatory cytokine release and monocyte adhesion in response to very low levels of endotoxin\textsuperscript{121}. In general, statin treatment reduces NF-\kappa B activation\textsuperscript{122}, inhibits the CD40-CD40 ligand expression\textsuperscript{38, 123} and decreases the matrix metalloproteinase levels in THP-1 monocytes\textsuperscript{124} and human carotid plaques\textsuperscript{125}, while treatment with rosuvastatin, atorvastatin and/or simvastatin increases the HDL-cholesterol level\textsuperscript{126}, which has both antioxidant and anti-inflammatory properties. These HDL-raising effects of statins may also relieve oxidative stress.

**Effects of Statins on Fatty Liver**

Although the effects of statins on the pathogenesis of NAFLD has not yet been clarified, many studies have demonstrated the beneficial role of statins in treating NAFLD. In a study with a small number of patients, a significant reduction of hepatic steatosis was noted among the subjects taking statins compared to that observed in those not taking statins\textsuperscript{127}. Furthermore, studies of various statins have demonstrated reductions in the levels of aminotransferases and hepatic lipids\textsuperscript{128-130}. However, one small pilot study comparing simvastatin monotherapy with non-statin treatment found no significant reductions in the aminotransferase levels, degree of hepatic steatosis, inflammatory activity or fibrosis, despite a 26% reduction in the LDL level associated with statin use\textsuperscript{131}. In contrast, rosuvastatin and pitavastatin treatment has been shown to improve metabolic parameters and liver histology in patients with fatty liver and dyslipidemia\textsuperscript{132, 133}. Of note, most of these trials were limited by a small sample size, their study design and the lack of control of confounding factors, such as lifestyle factors and the effects of concomitant drugs.

A limited number of studies have suggested pos-
sible mechanisms by which statins improve NAFLD and/or reduce the aminotransferase activity. For example, simvastatin inhibits the proliferation of hepatic stellate cells and decreases the expression of collagen I, III and IV. This drug also improves the prognosis of hepatic fibrosis by increasing the eNOS expression and decreasing the iNOS expression in an animal model of fatty liver. Because oxidative stress is one of the main causative factors underlying the pathogenesis of NAFLD, statins appear to play a protective role against the progression of NAFLD via their antioxidant properties.

Statins are also effective in reducing the levels of biomarkers, such as TNFα, IL6 and C-reactive protein, which are indicative of an advanced histology of NASH. Atorvastatin improves the disease activity via its TNFα-lowering effects in biopsy-proven NASH patients, and rosuvastatin significantly ameliorates hepatic lobular inflammation by decreasing the hepatic mRNA expression of TNFα and IL6.

Some statins increase the adiponectin level, which may decrease FFA delivery to the liver and thus slow the progression of steatosis. A recent study demonstrated that atorvastatin therapy prevents diet-induced lipid accumulation in the liver in guinea pigs via the downregulation of hepatic CD36 proteins, which subsequently facilitates the hepatic uptake of lipids. In a diet-induced fatty liver animal model, rosvustatin was found to ameliorate hepatic fibrosis in association with a decrease in the hepatic mRNA expression of TGF-β, connective tissue growth factor and type-1 procollagen.

Therefore, both in vitro and in vivo studies suggest that statins play a protective role in the development and progression of NAFLD via various mechanisms. However, further mechanistic studies are warranted to clarify the exact roles of statins in this field.

**Association between Statin Treatment and the Progression of Insulin Resistance and T2DM**

Although statins have been proven to be effective in reducing CVD, conflicting data exist regarding the effects of some statins on the risk of incident T2DM. Interestingly, a meta-analysis of randomized controlled trials suggested potential differences between individual statins, with pravastatin showing a trend toward reducing metabolic risks and atorvastatin, rosuvastatin and simvastatin together being associated with a significantly increased risk of T2DM vs. a placebo. More recent analyses have demonstrated an increased incidence of diabetes following statin treatment, regardless of the statin type. High doses of statins reduce the risk of cardiovascular events, although they also tend to increase the risk of T2DM.

The mechanisms by which statins increase the risk of T2DM have not been fully elucidated. However, statins may decrease the production of metabolites of HMG-CoA, such as isoprenoids, which upregulate insulin-responsive glucose transporter (GLUT)-4, thereby enhancing glucose uptake. Lovastatin, atorvastatin and simvastatin decrease isoprenoid synthesis and downregulate GLUT-4 production, thus inducing a reduction in insulin sensitivity.

**Effects of Individual Statins on the Adiponectin Levels**

Adiponectin, an insulin sensitizing adipocytokine linked to the redox system, may have an effect on the statin-adiponectin-insulin resistance relationship. For example, treatment with the globular domain of human adiponectin suppresses glucose-induced ROS in a dose-dependent manner up to 81%. In an in vitro study, treatment of endothelial cells with human adiponectin inhibited the release of oxidized LDL-induced superoxide, indicating that adiponectin suppresses cellular superoxide generation, possibly via an NAD(P)H oxidase-linked mechanism.

Individual statins may have different effects on the circulating and/or expression levels of adiponectin. Statins that increase adiponectin may have beneficial metabolic effects, such as improvements in the vascular actions of insulin, decreases in inflammation and reductions in endothelin-1 secretion in the endothelium. For example, pravastatin and pitavastatin both improve insulin sensitivity by increasing the circulating adiponectin levels in humans. In contrast, other statins, particularly when administered at high doses, result in unfavorable effects, such as reductions in insulin secretion and the exacerbation of insulin resistance. For example, in one study, the blood glucose levels, as determined on oral glucose tolerance tests, were higher in the group treated with atorvastatin for six weeks than in the control group.

In another study, simvastatin (20 mg) treatment significantly decreased the plasma adiponectin levels and insulin sensitivity, while pravastatin (40 mg) treatment significantly increased the plasma adiponectin levels and insulin sensitivity at equal lipid-lowering doses. In contrast, neutral effects of pitavastatin on glucose homeostasis were observed in two cohorts of subjects with metabolic syndrome, independent of the efficacy of this drug in reducing LDL. Most recently, the J-PREDICT study showed that pitavastatin treatment reduces the incidence of T2DM in Japanese subjects.
with prediabetes by 18% over three years (Odawara M, Pitavastatin and incident T2DM; 5th Scientific Meeting of the Asian Association for the Study of Diabetes, 2013, Seoul, Korea). Therefore, differences in the metabolic actions of individual statins may be mediated by adiponectin, which is implicated in ROS production and oxidative stress. Therefore, the risk of inducing insulin resistance and benefits in reducing cardiovascular risks should be considered in an integrated fashion.

Conclusions

The worldwide obesity epidemic is driving enormous increases in the incidence of cardiometabolic disorders. Along with insulin resistance, atherogenic dyslipidemia, endothelial dysfunction, activation of the renin-angiotensin system, endoplasmic reticulum stress and dysregulation of the redox system with resulting low-grade inflammation appear to play a role in the development of cardiometabolic disorders. There is now compelling evidence that statins have the ability to prevent dysregulation of the redox system by reducing the oxidative stress that contributes to these conditions. Therefore, further studies focusing on the effects of statins beyond their LDL-lowering actions are clearly warranted.

Funding Sources

This study was supported by Seoul National University Bundang Hospital (B-1405/250-005).

Disclosures

Dr. Barter has received honoraria and/or research funding from Astra Zeneca, Kowa, MSD, Pfizer, Roche, Amgen, Novartis, Sanofi-Regeneron and CSL Behring. The other author declares that he has no relevant financial interests.

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