FORUM REVIEW ARTICLE

Differential Metabolic Actions of Specific Statins: Clinical and Therapeutic Considerations

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Abstract

Significance: Statins, the most widely prescribed drugs in clinical practice, mainly act by reducing the plasma level of low-density lipoprotein (LDL)-cholesterol. A shift in redox homeostasis to an imbalance between reactive oxygen species generation and endogenous antioxidant mechanisms results in oxidative stress that has been implicated in the pathogenesis of various diseases, including those of the cardiovascular system. Beyond their efficacy in lowering LDL cholesterol, statins modulate redox systems that are implicated in the development of atherosclerosis, cardiovascular morbidity, and mortality. **Recent Advances:** Differences in specific statins or their dosages result in differential metabolic actions arising from off-target or unknown mechanisms of action that can have important implications for overall patient morbidity and mortality. **Critical Issues:** A recent meta-analysis and a combined analysis have suggested that high doses of statins increase the risk of developing type 2 diabetes mellitus, but reduce the risk of cardiovascular events. Thus, it is important to consider the cardiovascular and metabolic context and natural history of diseases when choosing a specific statin therapy for optimal individual patient health over the long term. **Future Directions:** More information is needed regarding the metabolism of statins, and the off-target or unknown actions of statins in affecting insulin resistance and metabolic homeostasis. The differential metabolic effects of specific statins should be considered in formulating optimal therapeutic strategies to reduce not just cardiovascular-related but also overall patient morbidity and mortality. *Antioxid. Redox Signal.* 20, 1286–1299.

Introduction

STATIN THERAPY is effective for lowering cholesterol and decreasing cardiovascular morbidity and mortality. Currently, statins are taken by more than 25 million individuals worldwide with the aim of reducing the risks of cardiovascular disease and death (5). Statins bind directly to 3-hydroxy-3-methylglutaryl CoA (HMG-CoA) reductase to impair endogenous cholesterol synthesis.

Interestingly, some studies suggest that statins have beneficial effects on the cardiovascular system beyond lowering the circulating level of low-density lipoprotein (LDL)-cholesterol (35, 43, 44, 45, 47, 63, 66, 100, 101). Since

inflammation is closely linked with oxidative stress and the production of reactive oxygen species (ROS) (2, 33), the antiatherogenic effects of statins, beyond lowering LDL-cholesterol levels, seem to be related to their ability to reduce ROS production and/or activities. A number of studies have shown that statins have anti-inflammatory and antioxidative properties (37, 52, 54, 62, 63, 65, 69). It has been shown *in vitro* and *in vivo* that statins inhibit lipid and lipoprotein oxidation, thereby inhibiting ROS formation or blunting the damaging effects of these free radicals (44, 108, 110).

It is now known that differences in specific statins or dosages thereof result in differential metabolic actions arising *via* off-target or unknown mechanisms of action which can have

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important implications for overall patient morbidity and mortality (22, 49, 61, 84, 112). Thus, it is important to consider the cardiovascular and metabolic context and natural history of diseases when choosing specific statin therapies for optimal individual patient health over the long term. The worldwide obesity epidemic is driving enormous increases in the incidence of diabetes mellitus and its cardiovascular complications, which necessitate integration of both metabolic and cardiovascular responses to statins to determine the optimal choices and dosages of statins for individual patients. In this review, we discuss the differential cardiovascular and pleiotropic metabolic actions of specific statins. These are critical considerations influencing atherosclerosis, risk of diabetes mellitus, and modulation of insulin sensitivity that might help in predicting the overall morbidity and mortality in patients undergoing statin therapies.

Inflammation and Oxidative Stress in Endothelial Dysfunction and Insulin Resistance

Endothelial dysfunction is characterized by a decreased bioavailability of nitric oxide (NO). This might arise, in part, from enhanced NO catabolism secondary to increased superoxide anion production. Endothelial dysfunction is also characterized by increased synthesis and secretion of the peptide endothelin-1 from endothelial cells. One mechanism underlying this is oxidative stress, which generates a strong stimulus for increased expression of endothelin-1 in vascular smooth muscle and endothelial cells, resulting in enhanced vasoconstrictor tone and release of proinflammatory proteins (48). The transcription of many of these proteins is regulated by the transcription factor nuclear factor kappa-B (NF- κ B). Plausible mechanisms for these actions include the actions of

various substances such as angiotensin II (Ang II), proinflammatory cytokines, and free fatty acids that promote ROS generation in vascular endothelial cells and smooth muscle cells in response to injury through several mechanisms. Oxygen-derived free radicals activate NF- κ B to stimulate the transcription of proinflammatory genes in the nucleus. This results in the synthesis of proteins such as cell adhesion molecules, cytokines, and chemokines (Fig. 1) (44, 48, 85). In transgenic rats, increased levels of the angiotensin II type I (AT1) receptor, nicotinamide adenine dinucleotide phosphate (NADPH) oxidase activation, and ROS contribute to vascular insulin resistance, endothelial dysfunction, apoptosis, and inflammation (114). Under these conditions, production of the endogenous NO synthase (NOS) inhibitor asymmetric dimethylarginine reduces insulin sensitivity, consistent with previous observations that reduced NO levels play a unfavorable role in insulin sensitivity (103). Importantly, elevated levels of free fatty acids associated with insulin resistance, obesity, diabetes mellitus, and the metabolic syndrome cause endothelial dysfunction by activating innate immune inflammatory pathways upstream of NF- κ B (Fig. 1) (107). In particular, endothelial NOS (eNOS) plays a critical role in the regulation of endothelial function by producing NO. The bioavailability of eNOS-derived NO is crucial for this function, and might act at multiple levels (40). Thus, NOS uncoupling and tetrahydrobiopterin deficiency contribute to the inflammatory and abnormal cytokine milieu in the vasculature (71). Furthermore, hyperglycemia significantly elicits the expression of cytokine-inducible NOS (iNOS) both *in vitro* and *in vivo* (36, 118). Indeed, hyperglycemia induced by streptozotocin in *Nos2* gene knockout mice led to diabetic cardiomyopathy, and sepiapterin, an inhibitor of NOS uncoupling, improved systolic

FIG. 1. Many stimuli initiate the transcription of genes in the endothelium encoding protein mediators of inflammation and hemostasis. Angiotensin II (Ang II) binds to angiotensin II type I receptor (AT1R) to produce oxygen-derived free radicals. These dissociate inhibitory factor kappa-B (I κ B) and, thus, activate nuclear factor kappa-B (NF- κ B), which stimulates the expression of proinflammatory genes in the nucleus and the production of proinflammatory proteins such as chemokines and cytokines. Statins inhibit the expression of AT1Rs. They also inhibit production of oxygen-derived free radicals by reducing the level of low-density lipoprotein (LDL)-cholesterol, increasing nitrous oxide (NO) synthesis, and promoting antioxidant activities. Therefore, statins inhibit the action of NF- κ B and inflammatory protein production, and improve NO bioactivity. Modified from Koh and colleagues (44, 48, 50).

function, suggesting that iNOS uncoupling plays a major role in the pathophysiology of the diabetic heart (36). Thus, uncoupling of the various NOS isoforms, with decreased NO production and increased levels of superoxides, is one of the major causes of endothelial dysfunction found in subjects with diabetes mellitus, hypertension, and atherosclerosis.

The role of insulin in the development of atherosclerosis is still under debate. Some researchers believe insulin to be a growth factor with proatherogenic effects, while others view insulin resistance to be proatherogenic *per se*, rather than insulin itself (10). Recent data suggest that insulin may have both antiatherogenic and proatherogenic effects according to the individual's insulin resistance status (10). In the absence of insulin resistance, insulin enhances endothelial function by mediating phosphoinositide 3-kinase-Akt-endothelial NOS (42). This vasculoprotective action of insulin is known to disappear in an insulin-resistant state (15). In addition, insulin may have 'atherogenic' actions by enhancing vascular smooth muscle cell proliferation in an insulin-resistant milieu (42). Thus, inflammation and oxidative stress contribute to endothelial dysfunction and insulin resistance, whereas endothelial dysfunction and insulin resistance together promote oxidative stress and inflammation (41). Mechanisms contributing independently to both insulin resistance and endothelial dysfunction include glucotoxicity, lipotoxicity, and inflammation (Fig. 2) (31, 41, 42, 51). In metabolic and cardiovascular diseases associated with insulin resistance, impairment in the phosphatidylinositol 3-kinase branch of insulin-signaling pathways in both vascular and metabolic tissues contributes to synergistic coupling of insulin resistance and endothelial dysfunction (Fig. 3) (41). These reciprocal relationships between insulin resistance and endothelial dysfunction are present in the spontaneously hypertensive rat, a genetic model with characteristics of human metabolic syndrome (82, 83). In clinical studies, there are positive correlations between insulin resistance and low blood flow to insulin-sensitive tissues in diabetic and obese subjects (67).

Statins Act to Reverse Oxidative Stress and Inflammation

A large body of evidence from clinical studies suggests that statins have anti-inflammatory effects. Statin therapy reduces

the levels of C-reactive protein (CRP), a marker of inflammation and an independent risk factor for cardiovascular diseases (1, 89). In the pravastatin inflammation/CRP evaluation (PRINCE) study, pravastatin reduced CRP levels at both 12 and 24 weeks, independent of reductions in LDL-cholesterol levels (1). Another study among patients with acute coronary syndromes randomized to treatment with atorvastatin (80 mg) or pravastatin (40 mg) proved that the clinical effects of statins in patients with coronary heart disease depend on reductions in both LDL cholesterol and CRP (88). In the Justification for the Use of Statins in Prevention: an Intervention Trial Evaluating Rosuvastatin (JUPITER) trial, rosuvastatin treatment produced a 65% reduction in vascular events in participants who achieved both an LDL-cholesterol level of <1.8 mM and a high-sensitivity CRP level of <2 mg/L (89). These data provide evidence that statins have anti-inflammatory effects in addition to lipid-lowering effects. Statin treatments also reduce the levels of other atherogenic cytokines and improve proinflammatory processes. A study on human blood vessel explants has shown that atorvastatin inhibits both proinflammatory cytokine release and monocyte adhesion in response to very low levels of endotoxin (87). Statin treatment also reduces NF- κ B activation (25), inhibits CD40-CD40 ligand expression (98), and decreases matrix metalloproteinase levels in humans (20, 63). In isolated T cells from healthy subjects, lovastatin treatment inhibited production of the cytokines interleukin (IL)-2, IL-4, and interferon- γ from activated cells *via* down-regulation of both activator protein (AP)-1 and NF- κ B expressions in a dose-dependent manner (17). Simvastatin treatment reduced the expression of proinflammatory cytokines such as IL-6, IL-8, and monocyte chemoattractant protein-1 in peripheral blood mononuclear cells from patients with hypercholesterolemia (86). All these factors are associated with plaque progression and stability.

Statins are involved in the isoprenylation pathway. A potential mechanism for the inhibition of proinflammatory signaling by statins is associated with reduced synthesis of mevalonate, the immediate product of HMG-CoA reductase, rather than of cholesterol itself. Statins block the isoprenylation and activation of small guanosine-5'-triphosphate-binding proteins, such as RhoA and Rac1 (79). Rac1, in particular, might play a key role in the regulation of NADPH oxidase

FIG. 2. Shared and interacting mechanisms of glucotoxicity, lipotoxicity, and inflammation underlie reciprocal relationships between insulin resistance and endothelial dysfunction that contribute to linkages between metabolic and cardiovascular diseases. AGE, advanced glycation end product. Modified from Koh and colleagues. (31, 42).

FIG. 3. Reciprocal relationship between endothelial dysfunction and insulin resistance. (A) Parallel phosphoinositide 3 kinase (PI3K)-dependent insulin signaling pathways in metabolic and vascular tissues couple metabolic and vascular physiology synergistically under healthy conditions. **(B)** Parallel impairment in insulin signaling pathways under pathological conditions contributes to the coupling of insulin resistance and endothelial dysfunction. Modified from Koh and colleagues. (31, 41).

(109, 110), which is a major source of ROS. Statins attenuate oxidative stress by inhibiting Rac1 (79). Statins also have an indirect inhibitory action on NADPH oxidase *via* inhibition of Rac isoprenylation (9). In addition, statins decrease the mRNA expression of NADPH oxidase subunits and reduce NADPH oxidase activity, a major source of ROS in vascular walls (110). Atorvastatin protects against cerebral infarction *via* inhibition of NADPH oxidase-derived superoxide in situations of transient focal ischemia (34). Preoperative treatment with atorvastatin in patients undergoing coronary artery bypass grafting rapidly improves vein grafts' redox state by suppressing NADPH oxidase activity in vascular cells (3). This effect of statins on NADPH oxidase-derived reductions in ROS levels might serve to reduce the oxidative stress load on the vasculature.

Statin treatments decrease the levels of oxidized lipids as well as of circulating lipoproteins. A number of studies have demonstrated that therapies with statins directly inhibit LDL-cholesterol oxidation. Thus, LDL cholesterol isolated from patients treated with simvastatin was found to be protective against LDL oxidation (29). Fluvastatin has also been reported to inhibit LDL-cholesterol oxidation (117) and to scavenge free radicals directly and preferentially (91). Interestingly, a direct comparison between treatments with fluvastatin *versus* pravastatin showed that fluvastatin demonstrated a much greater inhibition of LDL-cholesterol oxidation than did pravastatin (91, 117). Moreover, metabolites of atorvastatin are effective at preventing LDL-cholesterol oxidation in both metal ion-dependent and -independent systems (4).

Statins have been shown in both human studies and animal models to up-regulate NOS-3 expression (111), which improves endothelial function (54, 64). In studies designed to determine the mechanism of eNOS up-regulation by statins, mevastatin therapy significantly increased the levels of both eNOS mRNA and protein in human endothelial cells (68).

In addition to NF- κ B, AP-1 is an important transcription factor that may mediate pathogenic effects brought on by an increased proinflammatory state. In a double transgenic rat model harboring the human genes for renin and angiotensinogen, cerivastatin treatment decreased mortality,

lowered blood pressure, preserved renal function, decreased cardiac hypertrophy, and inhibited a chain of inflammatory events. Furthermore, the activations of both NF- κ B and AP-1 were sharply attenuated. Cerivastatin might act by inhibiting prenylation, membrane anchoring, and subsequent activation of Ras proteins (23). FOXO (Forkhead O) transcription factors are a direct target of phosphatidylinositol-3 kinase/Akt signaling in skeletal and smooth muscle, and they regulate the expression levels of the Cip/Kip family of cyclin kinase inhibitors in other cell types. Lovastatin specifically recruits the forkhead box FoxO3a transcription factor to the cell cycle inhibitor p21 promoter, mediating transcriptional transactivation of the p21 gene in isolated primary cardiomyocytes. Lovastatin also stimulates protein kinase B/Akt kinase activity, and Akt-dependent phosphorylation promotes translocation of p21 into the cytoplasm, leading to inhibition of Rho kinases. This contributes to the suppression of cardiomyocyte hypertrophy. p21 functions as a downstream target of FoxO3a and helps mediate antihypertrophic responses to statins (32). The molecular mechanisms of how statins serve to reverse oxidative stress and inflammation have been elucidated in a number of experimental studies (Fig. 1).

Differential Metabolic Actions of Specific Statins

Residual cardiometabolic risk after statin treatment

Despite achieving very low levels of LDL cholesterol, many patients demonstrate cardiovascular disease progression with clinical cardiovascular events (73). One study evaluated seven clinical trials investigating the determinants of plaque progression in 3437 patients with coronary artery disease (CAD) who underwent serial intravascular ultrasound examination, concentrating on those achieving very low levels of LDL cholesterol (6). Despite achieving an LDL-cholesterol level of <70 mg/dl, in >20% of patients, atherosclerosis continued to progress. Multivariate analysis revealed that the independently associated risk factors for plaque progression included the baseline atheroma volume, the presence of diabetes mellitus, an increase in systolic blood pressure, a lower increase in high-density lipoprotein

(HDL)-cholesterol, and a smaller decrease in apolipoprotein B levels, but did not include changes in CRP or LDL-cholesterol levels. Thus, residual risk factors are associated with the likelihood of disease progression in patients who achieve very low LDL-cholesterol levels (49). In particular, insulin resistance, glucose intolerance, and other features of metabolic dysregulation might play a major role in this regard, mediated by their known effects on atherogenesis, platelet dysfunction, and proinflammatory states. The association between apolipoprotein B and atheroma progression highlights the importance of LDL particle size in patients with optimal LDL-cholesterol control. Indeed, several large-scale clinical trials have demonstrated the increased risk of vascular diseases associated with elevated levels of apolipoprotein B or non-HDL-cholesterol (8, 24, 77, 120).

According to analysis by the Emerging Risk Factors Collaboration, developing diabetes mellitus doubled the risk of developing CAD and ischemic stroke after accounting for other risk factors (94). In addition to vascular disease, diabetes mellitus is associated with substantially higher rates of premature death from cancer, infectious diseases, external causes, and degenerative disorders, independent of other major risk factors (99). Thus, large prospective clinical trials are required to compare the effects of specific statin treatments in subjects with metabolic disorders with regard to overall mortality as well as cardiovascular and metabolic morbidity and mortality. Without this information, it is difficult to draw evidence-based conclusions regarding the balance between the risks of adverse metabolic consequences of statins and their beneficial lipid-lowering effects on cardiovascular events. This is particularly problematic because diabetes mellitus and other metabolic diseases are major risk factors for cardiovascular complications. A rational approach for intensive modification of global risk factors in subjects with CAD (especially in the presence of metabolic dysregulation) is urgently needed (46, 74).

Different characteristics and metabolic effects according to type and dose of statins

The effects of statins in reducing cardiovascular morbidity and mortality may differ with individual statins. According to tissue selectivity, statins can be classified into hydrophilic and lipophilic forms. Indeed, lipophilic and hydrophilic statins have shown markedly contradictory effects on insulin resistance in many studies (16, 39, 49, 61, 115). Hydrophilic statins, such as pravastatin and rosuvastatin, are known to have fewer side effects because of their lower dependence on the cytochrome p450 enzyme (76). In a multicenter study on Japanese patients after acute myocardial infarction, treatment with hydrophilic pravastatin was superior to lipophilic statins in the prevention of new Q-wave appearance and in reducing the rate of adverse cardiovascular events (93). Another study showed that the beneficial effect of statins on the attenuation of inflammation and increase of adiponectin was due to their hydrophilicity (38). In contrast, lipophilic statins, particularly at high doses, cause unfavorable pleiotropic effects, including reductions in insulin secretion and exacerbation of insulin resistance (16). Lipophilic statins inhibit the synthesis of isoprenoids and suppress ubiquinone/coenzyme Q10 biosynthesis. Lipophilic statins might, thus, delay the formation of adenosine triphosphate by pancreatic β -cells, leading to im-

paired insulin secretion (61). Depending on the lipophilicity and dosage, treatments with lipophilic statins inhibit glucose-stimulated elevations of free Ca^{2+} in the cytoplasm of β cells, leading to impaired insulin secretion. Glucose-induced elevations in intracellular Ca^{2+} levels are attributable to an inflow of Ca^{2+} after activation of L-type Ca^{2+} channels in pancreatic β -cells. The potentially lipophilic simvastatin and moderately lipophilic simva acid, but not pravastatin, suppressed the glucose-induced elevation of intracellular Ca^{2+} level in lipophilicity- and dose-dependent manners (115). When the influence of statins on glucose-stimulated insulin secretion was evaluated by direct measurements, the potentially lipophilic simvastatin and moderately lipophilic simva acid but not pravastatin produced significant decreases in insulin release according to their lipophilicity and dosage (115).

The possibility of using lipophilic statins for reducing sensitivity to insulin was suggested by experiments using rats with streptozotocin-induced diabetes mellitus (39). The blood glucose level, as determined by oral glucose tolerance tests, was higher in the atorvastatin 6-week treatment group than in the control group. By contrast, pravastatin did not influence glucose tolerance. It is possible that lipophilic statins are taken up by the brain and fat tissue where they might cause unfavorable pleiotropic effects, including secondary actions on the regulation of insulin secretion and exacerbation of insulin resistance (61). Pravastatin, in contrast to lipophilic statins, improves insulin sensitivity and increases circulating adiponectin levels in humans, which might have beneficial metabolic effects as well as reduce atherogenesis by other than lipid-lowering mechanisms (e.g., improved vascular actions of insulin, decreased inflammation, and reduced endothelin-1 secretion by the endothelium). Rosuvastatin is less hydrophilic than pravastatin and increased the incidence of type 2 diabetes mellitus in a large clinical trial (89). Other mechanisms, including potential central nervous system actions of lipophilic statins to impair glucose homeostasis, might be important factors. In addition, statins might alter glycemic control differentially by decreasing the levels of various isoprenoids that enhance glucose uptake *via* glucose transporter-4 in adipocytes (30, 61). Taken together, it is true that the cardiovascular benefit of treatment with lipophilic statins outweighs the unfavorable metabolic risks. However, the beneficial effects of lipophilic statins on vascular health might be counterbalanced by their adverse metabolic effects, particularly when used for a long time.

We recently reported that hypercholesterolemic patients receiving rosuvastatin at 10 mg per day developed a significant mean elevation in hemoglobin A1c (HbA1c) levels from 5.73% to 5.79% over 8 weeks when compared with baseline (57). We also observed that simvastatin treatment significantly improved endothelium-dependent dilation, but reduced the adiponectin levels and insulin sensitivity in hypercholesterolemic patients (55). In another study, treatment with simvastatin (20 mg per day) significantly increased fasting insulin levels and decreased plasma adiponectin levels and insulin sensitivity, while treatment with pravastatin (40 mg per day) did not significantly change insulin levels but significantly increased plasma adiponectin levels and insulin sensitivity at equal lipid-lowering doses (Fig. 4) (56). Our group also reported that hypercholesterolemic patients receiving a high daily dose of atorvastatin (80 mg) developed greater insulin resistance, higher fasting insulin levels, and higher HbA1c levels when

FIG. 4. Effects of simvastatin and pravastatin treatment on plasma adiponectin levels and insulin sensitivity. Simvastatin treatment significantly decreased plasma adiponectin levels and insulin sensitivity compared with baseline. Pravastatin treatment significantly increased plasma adiponectin levels and insulin sensitivity compared with baseline. Moreover, these effects of pravastatin were significant when compared with placebo and simvastatin treatments. PI=placebo; S20=simvastatin 20 mg/day; P40=pravastatin 40 mg/day; QUICKI=Quantitative Insulin Sensitivity Check Index. Bars show the standard error of the mean. Reproduced with permission from Koh *et al.* (56).

compared with patients receiving the low dose of atorvastatin (10 mg) or placebo, suggesting that high-dose statin therapy might have greater adverse effects on glucose homeostasis than low-dose therapy (Fig. 5) (58).

Taken together, both lipophilic and hydrophilic statins produce cardiovascular benefits by lipid lowering. It is also true from current evidence that this beneficial effect of statins outweighs the unfavorable metabolic risks, particularly for lipophilic statins. However, this beneficial effect of lipophilic statins on vascular health might be counterbalanced by their adverse metabolic effects, particularly when used for a long time. The metabolic effects of statins are summarized in Table 1. Thus, the beneficial *versus* detrimental effects of specific statins on metabolic homeostasis need to be considered along with reductions in lipid levels *per se* to derive a therapeutic strategy that will reduce overall mortality and morbidity in different patient groups.

Statins and type 2 diabetes mellitus risk: clinical evidence

With current evidence, it is difficult to weigh the possible adverse metabolic effects of statins on overall mortality in a quantitative manner. In the West of Scotland Coronary Prevention Study (WOSCOPS), treatment of hypercholesterolemic men with pravastatin reduced their likelihood to progress to diabetes mellitus by 30% in 4.9 years (28). Further, the long-term follow-up (10 years extended from the original 5 years) of the WOSCOPS study group demonstrated that the risk of death from coronary heart disease, nonfatal myocardial infarctions, and rate of death from cardiovascular causes was significantly reduced with pravastatin treatment, suggesting that the impact of statin therapy on the dysregulation of metabolism may contribute substantially to overall mortality (27).

FIG. 5. Percentage changes in insulin level and in the QUICKI. Hypercholesterolemic patients receiving the higher dose of atorvastatin developed higher fasting insulin levels and greater insulin resistance than patients receiving the lower dose or placebo. Bars show the standard error of the mean. Reproduced with permission from Koh *et al.* (58).

TABLE 1. METABOLIC EFFECTS OF STATINS DOCUMENTED IN CLINICAL STUDIES

Drug	Daily dose, duration	Subjects' condition	Measurement	Result	Ref.
<i>Atorvastatin</i>					
	10, 20, 40, 80 mg, 2 months	Hypercholesterolemia	QUICKI	Decreases	(58)
			Adiponectin	Decrease	(58)
	10 mg, 90 days	Hyperlipidemia and impaired fasting glucose	HOMA-IR	No change	(11)
			Adiponectin	Increase	(11)
	20 mg, 12 weeks	Polycystic ovary syndrome	Malondialdehyde	Decrease	(96)
<i>Rosuvastatin</i>					
	20 mg, 6 months	Type 2 diabetes mellitus	HOMA-beta	Decrease	(7)
	10 mg, 12 weeks	High LDL-cholesterol	HOMA-IR	Increase	(78)
			Fasting insulin	Increase	(78)
	40 mg, 12 weeks	Familial combined hyperlipidemia	Insulin sensitivity by clamp study	No change	(105)
<i>Simvastatin</i>					
	20 mg, 6 months	Type 2 diabetes mellitus	HOMA-beta	Decrease	(7)
	40 mg, 12 weeks	High LDL-cholesterol	HOMA-IR	Increase	(78)
			Fasting insulin	Increase	(78)
	20 mg, 2 months	Hypercholesterolemia	QUICKI	Decrease	(56)
			Adiponectin	Decrease	(56)
<i>Pravastatin</i>					
	40 mg, 2 months	Hypercholesterolemia	QUICKI	Increase	(56)
			Adiponectin	Increase	(56)
	10, 40 mg, 2 months	Hypercholesterolemia	AUC of insulin	Decrease	(70)
<i>Pitavastatin</i>					
	2 mg, 12 weeks	Hypercholesterolemia with metabolic syndrome	HMW adiponectin	Decrease	(75)
	2 mg, 52 weeks	High LDL-cholesterol and glucose intolerance	Glucose metabolism	No change	(95)
<i>Fluvastatin</i>					
	20 mg, 12 months	Hypertension	HOMA-IR	Decrease	(104)
	80 mg, 6 weeks	Metabolic syndrome	Asymmetric dimethylarginine	Decrease	(81)

Ref., reference number; HOMA-beta and HOMA-IR, homeostasis model assessment of pancreatic β -cell function and insulin resistance, respectively; QUICKI, quantitative insulin check index; LDL, low-density lipoprotein; AUC, area under the curve; HMW, high molecular weight.

However, in the Women's Health Initiative study on 153,840 postmenopausal women aged 50–79 years, the primary prevention study reported that statins increased the risk of type 2 diabetes mellitus by 48% during 3 years of follow up (21). A recent meta-analysis reported that statin therapy was associated with a 9% increase in the risk of developing diabetes mellitus (97). In a different context, in a meta-analysis investigating the effects of lowering of LDL cholesterol in low-risk subjects, reduction of the LDL-cholesterol level with a statin reduced the risk of major vascular events (relative risk, RR, 0.79; 95% confidence interval, CI, 0.77–0.81, per 18 mg/dl reduction in LDL-cholesterol), largely irrespective of age, sex, baseline LDL-cholesterol level, or previous vascular disease, and also reduced the risks of vascular and all-cause mortality (18). Another recent meta-analysis and a combined analysis suggest that high doses of statins can increase the risk of developing type 2 diabetes mellitus, but reduce the risk of cardiovascular events (84, 113). Indeed, compared with moderate-dose statin therapy, the number needed to treat per year for a statistically valid measure of intensive-dose statin therapy was 498 for patients with new-onset diabetes mellitus, whereas the number needed to treat per year for intensive-dose statin therapy was 155 for cardiovascular events (84). These data seem to support the conclusion that the lipid-

lowering effects of statins outweigh their adverse metabolic effects. However, it is important to consider average 5-year follow up and statin interventions that are given early or late in the natural history of diabetes mellitus. In this regard, a recent study should be highlighted. Using a retrospective epidemiological approach, the authors analyzed administrative claims data from Ontario, Canada, to examine the comparative risk of incident diabetes mellitus for different statins in users aged more than 66 years (13). They found that, compared with pravastatin, treatment with atorvastatin, rosuvastatin, or simvastatin—but not fluvastatin or lovastatin—was associated with an increased risk of incident diabetes mellitus in statin-naïve older patients. The risk of developing diabetes mellitus did not differ between patients with or without cardiovascular diseases. Importantly, in line with a previous meta-analysis (93), there was an association between the development of overt diabetes mellitus and the potency and dosage of statins (13).

Interestingly, a meta-analysis of randomized controlled trials suggests potential differences between individual statins, with pravastatin showing a trend toward a reduction in metabolic risk (RR, 0.84; 95% CI, 0.86–1.49; $p > 0.05$), and atorvastatin, rosuvastatin, and simvastatin together demonstrating a significant increased risk for diabetes mellitus (RR,

FIG. 6. Effects of simvastatin alone, combined therapy, and losartan alone on plasma adiponectin levels and insulin sensitivity. Percentage changes in adiponectin levels from respective pretreatment values after treatment with simvastatin alone, combined therapy, and losartan alone (Left). Percentage changes in QUICKI from respective pretreatment values after treatment with simvastatin alone, combined therapy, and losartan alone (Right). The combined therapy with simvastatin and losartan significantly increased adiponectin levels and QUICKI result compared with simvastatin and losartan alone. Bars show the standard error of the mean. Reproduced with permission from Koh *et al.* (54).

1.14; 95% CI, 1.02–1.28; $p < 0.05$) versus placebo (19). Thus, the risks of diabetes mellitus and of cardiovascular events and death should be considered in an integrated fashion (46, 74).

Cardiovascular benefits versus adverse metabolic effects

Lowering lipid levels with statin therapy unequivocally results in cardiovascular benefits in high-risk individuals. Nevertheless, a reduction in LDL cholesterol to target levels with statins does not eliminate the risk of cardiovascular diseases. In part, this might arise from dysregulation in metabolic homeostasis caused by statin treatment, as well as inadequate effects on residual risk factors such as LDL particle size, oxidized LDL, and non-HDL cholesterol. Moreover, treatments with lipophilic statins might be associated with higher rates of diabetes mellitus and insulin resistance. The implications of the balance between cardiovascular benefit and metabolic risk for overall long-term health and survival are not fully established. Several different interpretations on

this point are plausible. One possibility is that the cardiovascular risk from diabetes mellitus is modest in the first decade after diagnosis. As a result, the benefits of statin therapy increase over time, and the net cardiovascular benefits in high-risk individuals will still strongly favor the most potent statin therapy independent of metabolic risk in terms of all-cause mortality. Another possibility is that the increasing human life span, thanks to advances in medicine, might unmask adverse metabolic effects for some statins. Thus, statins with beneficial metabolic profiles used early in the natural history of a given disease will have measurable effects to decrease overall mortality in the long run in conjunction with the direct cardiovascular and atherogenic benefits of particular statins. Considering the great number of subjects in need of primary prevention of cardiovascular disease, the adverse metabolic consequences caused by some statins will present an increasing burden and have substantial health consequences. Thus, assessment of statin therapy to reduce overall morbidity and mortality should be integrated with the metabolic actions of statins with their lipid-lowering effects. Until

FIG. 7. Percentage changes in adiponectin levels (left) and in the QUICKI (right) from respective pretreatment values after treatment with atorvastatin alone, combined therapy, and fenofibrate alone. Used with permission from Koh *et al.* (53).

more data are available, physicians might need to monitor glucose levels regularly in patients with multiple risk factors taking statins, to check for the development of diabetes mellitus.

Future study directions

We speculate that the long-term adverse effects of new-onset diabetes mellitus might generate a relative increase in deaths when specific statins are compared with each other at equal lipid-lowering doses. So far, large clinical studies addressing this specific issue are lacking. One should also consider that intensive statin therapy might cause more adverse effects and, therefore, lead to differences in routine clinical care between those treated with intensive- and moderate-dose regimens (49, 73).

Large clinical trials are required with a primary outcome of all-cause mortality in a head-to-head comparison between various statins at equal lipid-lowering doses in patients at risk for diabetes mellitus. Without such data, it is not possible to quantify the overall benefits of particular statins with favorable metabolic consequences *versus* those with unfavorable metabolic consequences in terms of overall mortality. Nevertheless, it will be prudent for physicians to make evidence-based choices of statin therapy for patients with disorders of both lipid and glucose metabolism, which are increasingly frequent comorbidities.

Combination Therapy to Overcome Unwanted Metabolic Effects of Statins

Since hypertension, dyslipidemia, hyperinsulinemia, and the visceral adipose tissue are linked by complex reciprocal molecular interactions, it is logical to expect that blocking an interconnected pathway might provide multiscale benefits. Hypercholesterolemia and hypertension have a synergistic deleterious effect on coronary endothelial function that is associated with increased oxidative stress (92). Experimental studies have also shown an extensive crosstalk between dyslipidemia and the renin-angiotensin-aldosterone system (RAAS) at multiple steps. Statins down-regulate AT1 receptor density (80). Ang II binds to the AT1 receptor and stimulates proinflammatory gene expression and down-regulation of peroxisome proliferator-activated receptors- α/γ (PPAR α /PPAR γ) (106). Treatment with fenofibrate, a PPAR α agonist, opposes the elevated blood pressure response to Ang II infusion by decreases in oxidative stress and inflammation in the vascular wall (26). PPAR γ ligands reduce the levels of AT1 receptor mRNA and protein (102). In addition to any direct effects on endothelial NO production, PPAR ligands enhance endothelial NO bioavailability, in part by altering endothelial superoxide anion radical metabolism through suppression of NADPH oxidase and induction of Cu/Zn-superoxide dismutase. These findings further elucidate the molecular mechanisms by which PPAR ligands alter vascular endothelial function directly (12, 102). Indeed, combined therapies with statins or PPAR agonists and RAAS blockades show additive beneficial effects on endothelial dysfunction and insulin resistance when compared with monotherapy in patients with cardiovascular risk factors (Figs 6, 7) (53, 54), by both distinct and interrelated mechanisms (Fig. 1) (47, 60, 72). Therefore, it has been proposed that a combined therapy with

statins or PPAR agonists and RAAS blockers to target multiple therapeutic pathways might provide the optimal treatment (14, 47, 119).

Innovation

High doses of statins tend to increase the risk of developing type 2 diabetes mellitus, but reduce the risk of cardiovascular events. Thus, it is important to consider the cardiovascular and metabolic context when choosing a specific statin therapy for optimal individual patient health over the long term.

Based on the results from *in vivo* and *in vitro* studies, combining low-dose statin treatment with other therapies such as renin-angiotensin system blockers, PPAR agonists, or ezetimibe to achieve the same target LDL-cholesterol level would be more beneficial from cardiometabolic perspective compared to high-dose statin treatment alone.

Conclusions

We propose a simple but practical recommendation for statin choice. In patients with acute coronary syndrome, high doses of potent statins such as atorvastatin or rosuvastatin are recommended, because the impact of cardiovascular events is likely to be greater than the additional metabolic risks. If patients stabilize after 3 months, they can be switched to optimal doses of statins. In patients with stable angina or under primary prevention of heart disease, low doses of metabolically safe statins are recommended. Combining low-dose statin treatment with other therapies such as RAAS blockers, PPAR agonists, or ezetimibe to achieve the same target LDL-cholesterol level might allow for the beneficial cardiovascular effects of lowering LDL cholesterol while minimizing adverse outcomes from high-dose statin treatment (74). However, the risks of possible side effects from combination therapy—such as myopathy when statin and fibrate are combined—should be taken into account. Randomized clinical trials to identify the efficacy of these approaches on reducing the risk of developing diabetes mellitus are urgently needed. The cost effectiveness of these combinations should also be evaluated. To define who is more vulnerable to developing diabetes mellitus or suboptimal glucose homeostasis, genetic or pharmacogenetic testing approaches for evaluating the risk of developing diabetes mellitus are also needed. In particular, more mechanistic information is required regarding the metabolism of statins and the off-target or unknown actions of statins and their impact on insulin resistance and metabolic homeostasis. These differential metabolic effects of specific statins are important considerations in formulating optimal therapeutic strategies for patients to help reduce overall morbidity and mortality and not just cardiovascular morbidity and mortality.

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Abbreviations Used

Ang II = angiotensin II
 AP = activator protein
 AT1 = angiotensin II type I
 CAD = coronary artery disease
 CI = confidence interval
 CRP = C-reactive protein
 eNOS = endothelial NOS
 HDL = high density lipoprotein
 HMG-CoA = 3-hydroxy-3-methylglutaryl CoA
 iNOS = inducible NOS
 IL = interleukin
 LDL = low density lipoprotein
 NF- κ B = nuclear factor kappa-B
 NO = nitric oxide
 NOS = nitric oxide synthase
 PPAR α /PPAR γ = peroxisome proliferators-activated
 receptors- α / γ
 QUICKI = Quantitative Insulin-Sensitivity
 Check Index
 RAAS = renin-angiotensin-aldosterone system
 ROS = reactive oxygen species
 RR = relative risk
 WOSCOPS = West of Scotland Coronary Prevention
 Study