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ORIGINAL ARTICLE

Lipid-lowering Therapies, Glucose Control and Incident Diabetes: Evidence, Mechanisms and Clinical Implications

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Abstract Lipid-lowering therapies constitute an essential part in the treatment and prevention of cardiovascular diseases and are consistently shown to reduce adverse cardiovascular outcomes in wide-scale populations. Recently, there is increased awareness of the possibility that lipid-lowering drugs may affect glucose control and insulin resistance. This phenomenon is reported in all classes of lipid-modifying agents, with differential effects of distinct drugs. Since the prevalence of metabolic syndrome and diabetes is rising, and lipid-modifying therapies are widely used to reduce the cardiovascular burden in these populations, it is of importance to examine the relationship between lipid-lowering drugs, glycemic control and incident diabetes. In the current review we discuss the evidence, ranging from experimental studies to randomized controlled clinical trials and meta-analyses, of how lipid-modifying therapies affect glycemic control and insulin sensitivity. Cumulative data suggest that both statins and niacin are associated with increased risk of impaired glucose control and development of new-onset diabetes, as opposed to bile-acid sequestrants which display concomitant moderate lipid and glucose lowering effects, and fibrates (particularly the pan-PPAR agonist bezafibrate) which may produce beneficial effects on glucose metabolism and insulin sensitivity. Ezetimibe is implied to ameliorate metabolic markers such as hepatic steatosis and insulin resistance, with yet little support from clinical trials, while fish oils which in experimental studies produce favorable effects on insulin sensitivity, although studied extensively, continue to show inconclusive effects on glucose homeostasis in patients with diabetes. Suggested mechanisms of how lipid-modifying agents affect glucose control and their clinical implications in this context, are summarized.

Keywords Lipid-lowering therapies · Diabetes · Glycemic control · Insulin resistance

Abbreviations

BAS	bile acids sequestrants
CETP	Cholesteryl ester transfer protein
CI	confidence interval
FPG	fasting plasma glucose
FXR	farnesoid X receptor
GLP-1	glucagon-like peptide-1
HDL-C	high-density lipoprotein cholesterol
HgbA1c	glycosylated hemoglobin
LDL-C	low-density lipoprotein cholesterol
n-3 PUFA	omega-3 poly-unsaturated fatty acids
PPAR	peroxisome proliferator-activated receptor
RR	relative risk
TGR5	G protein coupled bile acid receptor 1 (TGR5/GPBAR1)

Introduction

Cardiovascular diseases are a leading cause of morbidity and mortality in the developed world, and plasma lipid abnormalities are important risk factors which can be modulated by drug therapy [1]. Several classes of lipid-lowering drugs were developed in recent decades and entered clinical practice, of which statins are the most widely used and are proven to

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significantly reduce major cardiovascular events in both primary and secondary prevention. Over the years, numerous studies in all classes of lipid-lowering drugs, ranging from experimental animal models to randomized controlled trials in humans, have demonstrated that lipid altering medications may affect glucose control and insulin sensitivity, and thus may have important implications in patients with metabolic syndrome and diabetes, as well as in non-diabetic subjects. This may be in part due to the close relationship between lipid and glucose metabolism. However, not infrequently, mechanistic and clinical studies have reported conflicting results concerning the effects of lipid-lowering drugs on glucose and insulin homeostasis. As the prevalence of metabolic syndrome and diabetes is rising and expected to increase the burden of cardiovascular diseases, of which lipid-lowering drugs are a mainstay of treatment, it is important to evaluate the cumulative data on the influence of drugs designed to treat dyslipidemia on glucose control and incidence of diabetes, and assess their clinical significance.

In the current review we aim to discuss both the clinical evidence and suggested mechanisms of how lipid-lowering therapies affect glucose control and insulin resistance in both patients with and without diabetes (Table 1). In addition to statins, which recently raised the awareness to the link between medications and diabetogenic effect, we will refer also to nicotinic acids, bile acid sequestrants, fibrates, fish oils, ezetimibe and cholesteryl ester transfer protein (CETP) inhibitors.

Statins and the Risk of Diabetes

Lowering low-density lipoprotein cholesterol (LDL-C) by statins (HMG-CoA reductase inhibitors) reduce the risk of major cardiovascular events in a wide range of individuals, including patients with diabetes [2–5]. However, in recent years accumulating data including several meta-analyses have demonstrated a relationship between the use of statins, elevation of blood glucose levels and incidence of type 2 diabetes.

Evidence from Clinical Trials

Early statin trials did not include new-onset diabetes or hyperglycemia as an endpoint, and the results of studies evaluating the influence of statin therapy on glucose regulation were initially inconsistent. Data from a post-hoc analysis of the WOSCOPS study (West of Scotland Coronary Prevention Study) published in 2001, first suggested that pravastatin therapy might reduce the frequency of new-onset diabetes [6]. However, the definition criteria of diabetes in this study were different from normal clinical practice. In contrast, in the JUPITER trial (Justification for the Use of Statins in Prevention: an Intervention Trial Evaluating Rosuvastatin), evaluating rosuvastatin in subjects with elevated c-reactive protein for primary prevention of vascular events, statin treatment was associated with an increase of 25 % in physician-diagnosed diabetes compared to placebo, although without a significant increase in glucose levels and a very modest increase in glycosylated hemoglobin (HgbA1c) of 0.2 % [7].

The observation of increased diabetes risk in this trial attracted the attention of researchers to the possibility of glucose dysregulation by statin therapy. A meta-analysis presented in 2009, including 57,593 patients from 6 randomized controlled trials evaluating the effect of statin use on the risk of incident type 2 diabetes, observed a small increase in diabetes risk [relative risk (RR) 1.13, 95 % confidence interval (CI) 1.03–1.23], which was no longer significant when the WOSCOPS trial was included. The authors concluded that the relationship of statin therapy to incident diabetes remained uncertain [8]. A subsequent meta-analysis included 13 statin trials with 91,140 participants. Statin therapy was associated with a 9 % increased risk for incident diabetes, with little heterogeneity between trials [9]. The risk of development of diabetes with statins was highest in trials with older participants, and was generally low. Treatment of 255 patients with statins for 4 years resulted in one extra case of diabetes.

A more recent meta-analysis presented in 2011 investigated whether intensive-dose statin therapy is associated with increased risk of new-onset diabetes compared with moderate-dose statin [10]. Analysis included 5 statin trials with 32,752 participants without diabetes at baseline. Intensive-dose statin therapy was associated with an increased risk of new-onset diabetes compared with moderate-dose statin therapy. Odds ratios were 1.12 (95 % CI, 1.04–1.22) for new-onset diabetes and 0.84 (95 % CI, 0.75–0.94) for cardiovascular events for participants receiving intensive therapy compared with moderate-dose therapy, suggesting a dose dependent effect. The authors calculated number needed to harm, with respect to new-onset diabetes, which was 498 per year of intensive dose statin therapy, while the number needed to treat to prevent cardiovascular events with the same therapy was 155. Additional study, comparing high-dose atorvastatin to pravastatin therapy, had also been associated with worsening glycemic control with the more potent statin [11]. In another study, atorvastatin treatment was shown to increase fasting plasma glucose (FPG) and HgbA1c in a dose dependent manner; Atorvastatin 10 mg compared to 80 mg, resulted in a mean increase of HgbA1c of 2 % versus 5 % and FPG of 25 % versus 45 %, respectively [12]. A retrospective large cohort study found an increased risk of new-onset diabetes in those treated with statins (HR 1.2; 95 % CI 1.17–1.23), association that was consistent across types of statins and increased with the duration of use and cumulative dose. However, less significant association was observed with fluvastatin and pravastatin [13]. In addition, a recent large

Table 1 Key effects of lipid-lowering medications on glycemic control and their clinical implications

Lipid-lowering Medications	Key effects on glycemic control
Statins	• Increased incidence of new-onset diabetes; mild elevation of HgbA1c and FPG.
	• Dose dependent and potency effect.
	• Pravastatin and Pitavastatin suggested having less diabetogenic effect and positive impact on insulin sensitivity.
	• Baseline impaired fasting glucose, older age and multiple components of the metabolic syndrome are risk factors for statin induced diabetes.
	• Benefits of reducing cardiovascular events in patients at risk outweigh significantly the potential risk for developing new-onset diabetes or worsening glycemic control
Bile acids sequetrants	• Combined glucose and lipid lowering effects in diabetes. Reduction in HgbA1c, FPG and LDL-C levels, of moderate extent.
	• Colesevelam approved by FDA as an adjunct therapy to improve glycemic control in type 2 diabetes, in addition to its effect on lipid control.
	• Not associated with increased risk of hypoglycemia or weight gain.
Niacin	• Elevation of FPG levels; modest increase in HgbA1c.
	• More prominent glycemic effect in diabetic patients. Glucose levels are usually controlled by adjustment of anti-diabetic therapy.
	• Less prominent glucose dysregulation effect with lower dosages, extended-release regimens, and gradual titration.
	• Increase in glucose levels was reported in several studies to be transient and reversible with continuation of therapy.
Fibrates	• Bezafibrate reduce FPG and HgbA1c in dyslipidemic patients with diabetes.
	• Bezafibrate produce beneficial effects on glucose metabolism via PPAR-gamma activation.
	• Mixed results with other fibrates, attributed to selective PPAR-alpha activation in comparison to the pan-PPAR activation by bezafibrate.
n-3 PUFA (Fish-oils)	• Early reports connected high-dosage of fish oils with deterioration in glycemic control.
	• Experimental studies indicate fish oils to improve insulin sensitivity.
	• Studies show mixed results regarding risk of diabetes and deterioration of glycemic control.
	• Large data analyses continue to be inconclusive, but suggest no major harmful or beneficial associations between fish oils and the development of diabetes.
	• Inconsistency in results due to variations in type, amount and duration of fish oils consumed, preparation methods, levels of contamination, and differences between geographical regions.
Ezetimibe	• Inhibition of intestinal cholesterol absorption may ameliorate glycemic control and insulin sensitivity, especially in metabolic disorders such as obesity and hepatic steatosis. Human studies are yet small and report inconclusive results.
	• Clinical trials are mostly combination trials with statins, thus more difficult to assess the individual impact of ezetimibe on glycemia.

meta-analysis of randomized controlled trials investigating the impact of different types of statins on new-onset diabetes, concluded that pravastatin therapy was associated with the lowest rate of new-onset diabetes compared with other statins [14]. Furthermore, a review of 16 studies of patients receiving various statins, showed that as a class statins had no significant impact on insulin sensitivity compared with control. However, individually, pravastatin significantly improved insulin sensitivity [15].

Thus, there may be a moderating role for pravastatin on glucose levels related to its positive effects on insulin sensitivity, or possibly related to a lower dose or potency effect compared to other statins in the above trials. It should also be noted that several small studies suggest that pitavastatin may be associated with less diabetogenic effect, which is currently assessed in Japan in the J-PREDICT trial [16–18]. The influence of statins on dysregulation of glycemic control was also recently suggested in the diabetic population, demonstrating a small but statistically significant increase from baseline in HgbA1c levels of 0.3 % in dyslipidemic diabetic patients treated with high dose of potent statins for 18 weeks [19].

The relation between statins and incident diabetes has not been described in many population and observational studies. Data from 345,417 subjects from the Veterans Affairs database was used to study the change in FPG over a mean time of 2 years in patients with and without statin therapy. The adjusted change in FPG in non-diabetic statin users was +7 mg/dl and for diabetic statin users it was +39 mg/dl (a small but significant difference than non-statin users), concluding that statins are associated with a rise of FPG in patients with and without diabetes [20]. A more recent observational study investigating whether the incidence of new-onset diabetes is associated with statin use was conducted among 153,840 postmenopausal women participating in the Women's Health

Initiative [21]. Statin use at baseline was associated with a significant increased risk of diabetes (adjusted HR 1.48; 95 % CI, 1.38–1.59), and was observed for all types of statins. However, several potential confounders characteristic to observational studies may have influenced the results of this study, such as a higher baseline risk for developing new-onset diabetes in patients that were indicated for an initial treatment with statins.

A recent analysis of the JUPITER trial, addressed the concern of whether the cardiovascular benefits of treatment with statins exceeds the diabetes risk in the lower-risk primary prevention setting in which statin use have been progressively increasing [22]. Trial participants with no major diabetes risk factors had no increase in diabetes, while participants with ≥1 diabetes risk factors had an increase in the incidence of diabetes (HR 1.28, 95%CI 1.07–1.54). For those with diabetes risk factors, a total of 134 vascular events or deaths were avoided by statin treatment for every 54 new cases of diabetes diagnosed. In an analysis limited to the individuals who developed diabetes during follow-up, cardiovascular risk reduction associated with statin therapy (HR 0.63, 95 % CI 0.25–1.60) was consistent with that for the trial as a whole. By comparison with placebo, statins accelerated the average time to diagnosis of diabetes by only 5.4 weeks.

An analysis of several randomized trials with atorvastatin, demonstrate similarly in secondary prevention cohorts that baseline FPG levels and features of the metabolic syndrome (elevated BMI, hypertension, high triglyceride levels) are independent predictors of new-onset diabetes [23]. High-dose (atorvastatin 80 mg) compared with lower-dose statins, increased the risk of new-onset diabetes among patients with 2–4 diabetes risk factors by 24 %, but not in patients with 0–1 risk factors. The number of cardiovascular events was significantly reduced with statins in both diabetes risk factors groups [24].

Plausible Mechanisms for the Diabetogenic Actions of Statins

Although there is no definite proof for causal relationship between statins and glucose dysregulation, in the absence of proven residual confounding factors biasing the results, it is reasonable to assume that molecular mechanisms exist by which statins impair glucose metabolism. However, although several plausible explanations exist, the causal relationship is not yet fully understood.

Experimental studies demonstrate variable effects of statins on insulin secretion and sensitivity. It is suggested that the decrease in the availability of isoprenoids by statin therapy may lead to a reduction in insulin sensitivity [12, 25]. However, studies also have shown a protective effect of statins on insulin sensitivity [26, 27]. A systematic review of the effects of statins on insulin sensitivity did not demonstrate a consistent class effect, but suggested differences between individual statins with pravastatin least associated with worsening insulin sensitivity [15]. Compared to pravastatin, lipophilic statins have shown to decrease insulin secretion [28, 29]. Overall, there are conflicting results concerning the effects of statins on insulin secretion and sensitivity.

Researchers suggest a possible effect of statins on insulin signaling in peripheral tissues. Animal models have shown that statin-induced myopathy results in impaired signaling of PI3k/Akt and up-regulation of Foxo1 transcription factors in skeletal muscle, associated with the development of muscle insulin resistance [30]. Statins contribute to the depletion of products synthesized from the mevalonate pathway (Fig. 1). Reduction in ubiquinone (CoQ10) may result in mitochondrial damage, delayed ATP production, and thereby impaired insulin release [31]. Statins were also shown to decrease the expression of glucose transporter (GLUT4) in adipocytes by inhibiting isoprenoid biosynthesis, which may result in impaired glucose tolerance [32]. In addition, statins, via chronic

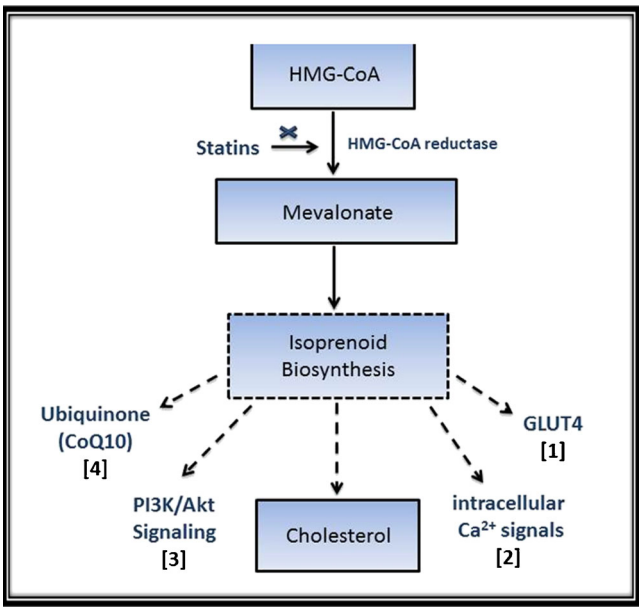

Fig. 1 Inhibition of the mevalonate pathway by HMG-CoA reductase inhibitors (statins), and suggested mechanisms leading to impaired glucose metabolism. Statins inhibit the rate-limiting step of the mevalonate pathway, a precursor for isoprenoids and cholesterol biosynthesis, leading to inhibition of the synthesis of isoprenoid intermediates and thus modulation of various signaling pathways: (1) Down-regulation and reduced expression of glucose transporter (GLUT4) in adipocytes, leading to cellular insulin resistance and reduction of insulin-stimulated glucose uptake. (2) Decrease in intracellular Ca^{2+} signals, altering Ca^{2+} homeostasis, leading to decreased Ca^{2+}-dependent glucose-induced insulin secretion. (3) Disruption of early insulin signaling, involving down-regulation of PI3k/Akt signaling and activation of FOXO transcription factors, may be associated with the development of muscle insulin resistance. (4) Suppression of ubiquinone (CoQ10) synthesis involved in the electron transfer system in the mitochondria, may result in delayed formation of ATP by pancreatic beta-cells leading to impaired insulin secretion

cholesterol depletion may contribute to inhibition of glucose-induced calcium signaling-dependent insulin secretion [28, 33].

Another potential explanation to the diabetogenic effects is that statins influence pancreatic beta-cells function, altering insulin secretion. It is suggested that an increase in oxidation of plasma-derived LDL-C due to statin-induced blockade of de-novo cholesterol synthesis may impair the intracellular immune response system. This may lead to pro-inflammatory and oxidative intracellular effects, which may contribute to the pathogenesis of diabetes during extended statin use, by compromising the functional and structural integrity of the islet beta-cells, leading to reduced insulin secretion [34].

Lastly, genetic predisposition to type 2 diabetes may also be a trigger to the effects of statins on glucose regulation in the presence of metabolic risk factors and insulin resistance. However, genome-wide studies have not yet identified associations between genes regulating HMG-CoA reductase and type 2 diabetes.

Conclusions and Clinical Implications

In view of the current data from the above published literature, the FDA recently included safety label changes to statin drugs, adding information concerning an effect of statins on incident diabetes and increase in HgbA1c and FPG levels [35].

Factoring in the cumulative evidence, the current data suggests that statins are associated with a modest consistent increase in the risk to develop new-onset diabetes, which is probably a dose–response relationship. Some data suggest a variation between the effects of different statins, which may be ascribed to the specific statin characteristics or possibly to its potency. However, the unequivocal life-saving benefits of statins in reducing cardiovascular events outweigh significantly the potential risk for developing new-onset diabetes or worsening glycemic control in patients who are at moderate or high risk for cardiovascular events. As statins are progressively used in lower risk and wider-scale populations over time, the risk of glucose dysregulation by statins may still be meaningful, and should be addressed and monitored in susceptible patients groups in which risk to benefit ratio may be increased such as older subjects, intensive-dose statin users, and patients populations for whom cardiovascular benefits of statins have not yet been proven. Individuals prone to statin-induced diabetes are shown to share major risk factors for diabetes as the general population, including multiple components of the metabolic syndrome and impaired fasting glucose, which requires drawing attention to lifestyle modification, monitoring blood glucose levels and diabetes risk assessment in patients at risk, while reassuring individuals without known risk factors for diabetes.

Bile Acid Sequestrants

Bile acids are synthesized in the liver by the oxidation of cholesterol. They are stored in the gallbladder between meals and secreted to the small intestine, facilitating absorption of dietary fat and lipid-soluble vitamins [36]. In the terminal ileum and colon the majority of the bile salts are reabsorbed and transported back to the liver through the enterohepatic circulation. Bile acids sequestrants (BAS) are non-absorbable resins that bind bile acids in the intestinal lumen, forming a complex secreted in the feces. They prevent the resorption of bile acids into the enterohepatic circulation, resulting in compensatory increase of bile acid synthesis in the liver, which depletes the hepatic cholesterol pool. This leads to up-regulation of hepatocyte LDL receptors, and enhanced delivery of LDL-C to the liver for the use in bile acid synthesis. The outcome of this process is a reduction in plasma LDL-C levels of 15–25 % in clinical trials. Accordingly, BAS have been used for many years in the treatment of dyslipidemia with high LDL-C levels, with proven clinical benefit in reducing the risks of coronary heart disease [37–39].

BAS and Glycemic Control – Clinical Evidence

Clinical data from several studies have suggested that BAS may improve glycemic control in type 2 diabetes. The improvement in glycemic control is probably a class effect. It was initially noted in a small study evaluating cholestyramine in diabetes, reducing plasma glucose levels by 13 % after 6 weeks of therapy [40]. Later, glucose lowering effects were demonstrated also with other BAS such as colestimide and colestilan [41, 42]. However, the most comprehensive data comes from reports on colesevelam hydrochloride, a second generation molecularly engineered BAS, which was approved by the US FDA in 2008 for the usage as an adjunct therapy to improve glycemic control in adults with type 2 diabetes, in addition to its effect on lipid control which is usually warranted in diabetes due to the high cardiovascular disease risk [43, 44]. Initially, the combined glucose and lipid lowering effects of colesevelam were observed in a pilot study randomizing type 2 diabetes patients to 3.75 g/day of colesevelam or placebo in addition to prior oral anti-hyperglycemic medications, showing significant reduction of HgbA1c (−0.5 %, placebo-corrected) as well as LDL-C levels in the BAS treated patients [45].

The addition of colesevelam to established anti-diabetes therapy was further evaluated in 3 larger randomized, double-blind, placebo-controlled trials [46–48]. In these trials, diabetic patients with inadequate glycemic control treated with several combinations of anti-diabetes agents were blinded to the addition of colesevelam treatment or placebo. The addition of colesevelam manifested in a statistically significant

placebo-corrected reduction of HgbA1c ranging from 0.50–0.54 %, which was accompanied by reduction in FPG relative to placebo in all 3 studies (placebo-corrected reduction of 13.5–14.6 mg/dl). Moreover, the addition of BAS in these trials was accompanied by significant LDL-C reduction (12.8–16.7 %, placebo-corrected). As seen with other BAS, an increase in triglyceride plasma levels was noted with the addition of colesevelam therapy. An important safety observation was that the addition of BAS was not associated in any of these studies with increased risk of hypoglycemia or weight gain. Additional studies with similar design were recently performed in patients with pre-diabetes and in non-diabetic men with metabolic syndrome, displaying modest improvement in glucose measures [49–51].

Based on the available data, recent diabetes consensus documents include colesevelam as a possible treatment option as part of combination therapy in type 2 diabetes, highlighting the advantages of LDL-C lowering and lack of hypoglycemic effects, in addition to relative disadvantages of generally modest HgbA1c lowering efficacy (and thus limited effect as monotherapy), constipation and increased triglyceride levels [52, 53].

Bile Acids and Mechanisms of Glucose Homeostasis

Bile acids have an important role in the regulation of energy, affecting glucose metabolism and homeostasis [36]. Bile salts activate nuclear receptors and signaling pathways such as the farnesoid X receptor (FXR) expressed in the liver and intestine, modulating transcription of genes involved in bile salts biosynthesis, cholesterol and glucose metabolism. In addition, bile acids bind and activate G protein coupled bile acid receptor 1 (TGR5/GPBAR1), resulting in kinase stimulation of cyclic adenosine monophosphate synthesis and transactivation of target gene expression. TGR5 is expressed in organs of the enterohepatic axis, and was shown to be expressed also in brown adipose tissue and skeletal muscle, implicating a role in energy homeostasis. Evidence exists for the role of bile acids in glucose metabolism. Studies have shown that bile acids pool size and composition are altered in diabetes, suggesting that diabetes impairs the normal regulation of FXR expression [54]. FXR was also suggested to play a role in insulin sensitivity regulation [55]. Additional evidence implicates a role for TGR5 in glucose control. Bile acids through TGR5 stimulate secretion of incretin hormone glucagon-like peptide-1 (GLP-1), affecting glucose homeostasis [56].

Corresponding to these roles of bile acids in energy homeostasis, several potential mechanisms are proposed to how BAS improves glycemic control (Fig. 2). BAS results in changes in bile salts pool composition, which may affect FXR and TGR5 activity and regulated pathways, translating to an increase in insulin sensitivity and insulin secretion [57, 58]. BAS may be able to modulate hepatic glucose metabolism via changes in FXR activity, affecting hepatic glucose homeostasis [59]. Furthermore, by decreasing bile acids reabsorption, BAS may increase luminal concentration of bile salts, activating TGR5, stimulating the release of GLP-1 and other incretin hormones into the blood, and thus increasing the sensitivity of pancreatic beta-cells to glucose and increasing glucose-stimulated insulin release. It has been demonstrated both in animal models and in diabetic patients, that BAS stimulate the release of post-prandial GLP-1, resulting in reduction of glucose levels [60–63].

Conclusions and Clinical Implications

Clinical studies have demonstrated that BAS provide both glucose and lipid lowering effects in adults with type 2 diabetes, including metabolic syndrome and early-diabetes cohorts. These combined benefits were evident mostly using colesevelam as an adjunct to other anti-diabetic treatments, showing modest but significant reductions in HgbA1c and FPG levels in diabetic patients, in parallel to a significant reduction in LDL-C. This was achieved with a low incidence of hypoglycemia, neutral effect on weight and satisfactory safety profile. The usage of BAS as part of drug combinations for achieving both lipid and glucose control, is a possibility which should be taken into account considering the cardiovascular risk equivalence of diabetes on the one hand, and the potential for deterioration in glycemic control using other lipid-lowering drugs on the other hand. However, both lipid and glucose lowering effects of BAS may be insufficient, requiring drug combination regimens.

Niacin

Nicotinic acid (niacin) is a water soluble vitamin-B3. It has combined beneficial effects on lipid profile, elevating HDL-C, lowering triglycerides and LDL-C levels, as well as lowering lipoprotein (a). The effects of niacin are dose dependent. In addition, niacin has pleiotropic effects including anti-inflammatory anti-thrombotic and anti-oxidant activity, which contribute to its clinical effects.

Over the years, several clinical trials have shown improved cardiovascular outcomes and regression of atherosclerosis with niacin treatment [64]. Recently, two large scale trials evaluating nicotinic acid compounds as an add-on treatment to statin and ezetimibe in subjects at vascular risk were terminated early due to side effects and lack of efficacy [65, 66]. This resulted in a significant reduction in the use of niacin in many countries. However, these two studies were conducted in subjects achieving very low LDL-C levels, and thus their

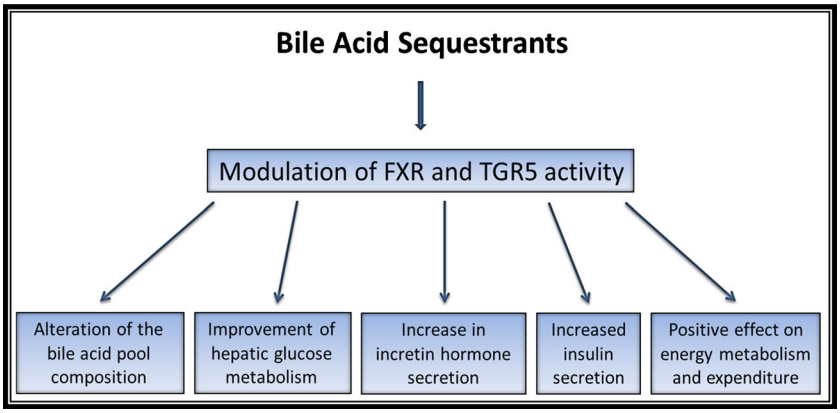

Fig. 2 Glucose-lowering Mechanisms of Bile Acid Sequestrants. BAS, in addition to their effect on lipids metabolism, have glucose-lowering effects. The plausible mechanisms behind these effects are suggested to be mediated through modulation of bile acid nuclear farnesoid X receptor (FXR) activity, and activation of membrane G protein-coupled receptor (TGR5) pathways. Most of the hypothesized mechanisms are based on animal studies

results may not be applicable to other populations, such as patients with familial hypercholesterolemia (most of which do not achieve treatment goals by statins alone). Additionally, the drug combination used in the HPS2-THRIVE trial, contained laropiprant (to reduce side effects of flushing), which might have been responsible for some of the side effects in this trial [66].

The potential benefits of nicotinic acid on lipid profile in humans were initially discovered in the 1950s [67]. Soon after, reports on the adverse effects of nicotinic acid on glucose tolerance and plasma insulin began to appear both in non-diabetic and diabetic populations [68, 69]. Since then, studies have consistently shown impaired glucose homeostasis during niacin treatment.

Niacin and Impaired Glucose Control – Clinical Evidence

Immediate-release nicotinic acid was demonstrated in older studies to result in a more significant deterioration in glycemic control in diabetic patients [70–74]. However, it is less used in recent years due to the high rate of adverse effects, especially flushing.

The development of extended-release niacin formulas resulted in lower rates of flushing and hepatotoxicity and enabled the use of lower doses of niacin in clinical practice. In the ADVENT trial (Assessment of Diabetic Control and Evaluation of the Efficacy of Niaspan Trial), dyslipidemic patients with stable type 2 diabetes were randomized to extended-release niacin or placebo [75]. FPG levels were elevated in the initial 1–2 months, but returned to baseline by 4 months of therapy. HgbA1c was increased slightly but significantly in the higher dose (1,500 mg) but not in the lower dose (1,000 mg) of niacin. A recent data analysis from the administrative-claims database did not show significant increase in anti-hyperglycemic treatment among stable type 2 diabetes patients treated with extended-release niacin, compared to other lipid-modifying therapies [76]. Niaspan, a prolonged release formulation of nicotinic acid, was evaluated in combination therapy with statin/ezetimibe treated patients, showing that addition of niacin produced small initial increases in FPG and new diagnoses of diabetes in the first 6 months of therapy that dissipated over time till the end of the study, largely without the use of anti-diabetic medications [77].

A meta-analysis including 30 randomized-controlled trials using niacin, reported hyperglycemia occurrence rate of 2.3 % in the niacin group versus 0.4 % in the control group (RR 3.04; 95 % CI 1.28 to 7.21, p=0.01) [78]. A more recent systematic review presented in 2008, assessing the effects of niacin on glycemic control in patients with dyslipidemia, concluded that the effects of niacin (≤2.5 g/d) on FPG (an increase of 4–5 %) and HgbA1c (an increase of ≤0.3 %) are modest and that niacin therapy was infrequently associated with incident diabetes or the need for new insulin prescriptions [79]. Researchers also combined lately the results of 5 previous clinical trials to evaluate the effect of niacin on glucose levels in subjects who had a baseline glucose level <100 mg/dl [80]. The use of niacin for 3 years was associated with an increase in blood glucose levels (9.9 versus 4.1 mg/dl, p=0.002) and the risk of developing impaired fasting glucose (38 % versus 21 %, p=0.003) compared to those not taking niacin, but not with the incident of diabetes mellitus.

In both recent niacin trials (Aim-High and HPS2-THRIVE), hyperglycemia was about twice as common as a reason for stopping randomized treatment in participants allocated to extended-release niacin than the placebo group [65, 66].

Acipimox, a less potent nicotinic acid derivative, inhibits lipolysis and the release of non-esterified fatty acids from adipose tissue. It is suggested to improve insulin sensitivity, and to exert potential "pleiotropic" effects [81, 82]. However,

evidence of clinical efficacy in the prevention of heart disease has not been well established.

Mechanisms Leading to Impairment in Glycemic Control

The mechanism of hyperglycemic actions of nicotinic acid is thought to involve insulin resistance. Studies demonstrated decreased insulin sensitivity in niacin treated subjects [83, 84]. Induction of insulin resistance with nicotinic acid was shown to be related to rebound elevation of circulating fatty acids [85]. This phenomenon of initial suppression of lipolysis in adipose tissue after nicotinic acid treatment, and then rebound elevation of free fatty acids, is thought to be associated with decreased expression of phosphoenolopyruvate carboxinase (PEPCK1) enzyme, which has a role in adipose tissue gluconeogenesis. Recent data additionally suggest that nicotinic acid alters cellular signaling and gene expression in insulin-sensitive tissues by various different mechanisms, such as changes in Akt or FOXO1 phosphorylation, which are involved in lipid and glucose metabolism [86]. Thus, increased insulin resistance in patients taking niacin may be the instigate to new-onset diabetes and impairment of glycemic control in diabetic patients.

Conclusions and Clinical Implications

The evidence accumulating over several decades support that nicotinic acid is associated in majority of studies with mild elevations of FPG levels and a modest increase in HgbA1c. The increase of glucose levels is in many cases dose-dependent and is less prominent with lower dosages, extended-release regimens, and gradual titration of the drug. The increase in FPG levels is generally transient and reversible with continuation of therapy. Patients should monitor glucose and HgbA1c levels periodically after niacin initiation and dosage increase, and be followed up for any deterioration in glycemic control, especially in patients who are at preliminary risk for new-onset diabetes. In infrequent cases of prolonged periods of worsening glucose homeostasis, a risk/benefit ratio should be weighed in each patient, taking into consideration the potential protective cardiovascular benefits of long-term niacin therapy, and the risks of hyperglycemia and diabetes.

Fibrates

Fibric acid derivatives (fibrates) are agonists of the peroxisome proliferator-activated receptors, selective for the alpha receptor (PPAR-alpha), a member of the ligand-activated nuclear hormone receptor superfamily. PPAR-alpha regulates fatty acid oxidation and lipid metabolism, controlling activity of genes that regulate energy homeostasis [87]. They increase transcription of lipoprotein lipase and major HDL apolipoproteins, and by that they are effective in treating dyslipidemia, lowering triglyceride levels and raising HDL-C. Fibrates have also been shown to reduce markers of inflammation, and inhibit mediators of endothelial dysfunction and thrombosis. The extent of effect of fibrates on cardiovascular events is controversial. A recent meta-analysis concluded that fibrates can reduce the risk of major cardiovascular events, but did not show reduction in mortality [88]. However, the cardiovascular effects of fibrates are augmented in high-risk individuals such as those with diabetic atherogenic dyslipidemia and metabolic syndrome [89]. Moreover, fibrate randomized controlled trials in patients with diabetes also demonstrate consistent and significant microvascular outcome benefits [90].

Mechanisms Connecting Fibrates With Glucose Regulation

Several fibrate drugs were developed over the years for clinical practice, including bezafibrate, ciprofibrate, clofibrate, fenofibrate and gemfibrozil. Bezafibrate, in comparison to other fibrates, is unique in activating all three PPAR subtypes (alpha, gamma and beta/delta) at comparable doses. PPAR-gamma is abundantly expressed in adipose tissue and regulates adipogenesis and glucose control. PPAR-gamma activation increases glucose uptake and synthesis by skeletal muscle and reduces hepatic glucose production. Accordingly, bezafibrate via PPAR-gamma may produce beneficial effects on glucose metabolism and insulin sensitivity [91]. Furthermore, PPAR-alpha which mediates the effects of fibrates on lipid metabolism may be also important in glucose regulation and improvement in insulin sensitivity, by reducing triglycerides and free fatty acids accumulation.

Evidence from Clinical Trials

Bezafibrate therapy in high triglyceridemic patients was shown to reduce insulin resistance and FPG levels [92–94]. Studies also demonstrated that bezafibrate may decrease the development and delay the onset of type 2 diabetes, and slow the progression of insulin resistance and beta cell dysfunction in diabetic patients [95–98]. In a recent large Japanese trial, bezafibrate significantly improved HgbA1c in dyslipidemic patients with diabetes. After 6 months of therapy, HgbA1c levels were decreased by 0.47 % in all the patients and by 0.76 % in patients with baseline HgbA1c levels ≥7.0 %. The rate of change in triglyceride levels was related to the changes in HgbA1c levels, and bezafibrate showed a potent effect in

reducing glucose levels regardless of concurrent anti-diabetes drug used [99].

Mixed results have been reported with fibrates other than bezafibrate, regarding their effects on glucose regulation and insulin sensitivity [100–114]. The variance in the results may be due to the more selective activation of PPAR-alpha in comparison to bezafibrate which is reported to act as a pan-agonist for all three PPAR isoforms. Thus, as fibrates exert their lipid-lowering activity via PPAR-alpha regulation of lipid metabolism, it is possible that similar to the insulin sensitizers glitazones, bezafibrate induce a direct effect on insulin sensitivity via PPAR-gamma. Furthermore, it may be that differences in PPAR-alpha distribution in insulin sensitive tissues vary between species, which may explain the observation that improved insulin sensitivity post-fibrate treatment was consistently seen in rodent models but less so in human studies [115, 116]. Large randomized controlled trials evaluating fenofibrate in type 2 diabetes did not demonstrate significant changes in glycemic control, as evaluated by HgbA1c, in comparison to placebo [117–119].

Since diabetes is associated with cardiovascular disease, attempts have been made to create dual PPAR alpha/gamma agonists, in order to target both glycemic control and atherogenic dyslipidemia in type 2 diabetes. Several such attempts have failed so far due to safety concerns. However, aleglitazar, a balanced dual PPAR alpha/gamma agonist, has shown promising results in initial phases of clinical trials [120].

Fish Oils

Long chain omega-3 poly-unsaturated fatty acids (n-3 PUFA) are essential fatty acids for growth and development. In human diet, the main source of n-3 PUFA is fish and fish oil supplements, predominantly in the form of eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA). Fish oils have been shown in dyslipidemic subjects to produce a significant dose dependent reduction in triglyceride levels ranging 20-50 %, which may be accompanied by mild increase in HDL and LDL cholesterol levels [121, 122]. Various additional potential beneficial effects on the cardiovascular system are attributed to fish oils, including anti-arrhythmic, anti-thrombotic and anti-inflammatory effects, lowering blood pressure and improvement in endothelial function [123]. Accordingly, numerous trials have demonstrated over the years positive effects of regular consumption of fish or supplements containing n–3 PUFA in various populations in health and disease, in particular in reducing the risk of cardiovascular events [124, 125].

Several systematic reviews and meta-analyses were published in this field in the last two decades, reporting conflicting findings. An early meta-analysis showed a strong positive effect of fish oils across all major cardiovascular outcomes, including mortality [126]. However, as larger randomized trials emerged, the magnitude of effect of fish oils was reduced in subsequent, more updated meta-analyses (which included more modern treatments of cardiovascular disease), reaching non-significance in recent systematic reviews [127–132]. The recently published large ORIGIN trial found that fish oils did not prevent death or any cardiovascular outcomes in high-risk patients for cardiovascular events who had (or were at high risk for) diabetes [133].

Fish Oils, Glycemic Control and Diabetes Mellitus

Early non-randomized trials starting the 1980s raised the concern that fish oils might be associated with deterioration in glycemic control [134–136]. In contrast, the results of population based studies suggested that fish and seafood intake may reduce the risk of impaired glucose tolerance and incidence of type 2 diabetes [137–141]. Results from published data further reported mixed results, varying from increased risk or no-association to decreased risk of diabetes with the intake of fish oils [142–147]. Variations in diet, in addition to the amount, duration, and fatty acid composition of fish oils contributed to the inconsistency of the results. Specifically, it was suggested that the negative effects of fish oils on glucose control in the initial studies, were due to very high doses of fish oils used in those trials. A direct association between the amount of fish intake and diabetes was observed in several studies, reporting a correlation between highest amount of fish consumed and risk for type 2 diabetes [148, 149].

Subsequently, several meta-analyses reported that fish oil supplementations have no significant effect on fasting glucose or HgbA1c in patients with diabetes [150, 151]. A systematic-review examined 27 fish oil trials to evaluate the impact of fish oils on blood glucose control in diabetes and non-diabetes patients. The investigators found a small non-significant net increase in HgbA1c and FPG but not in overall glucose homeostasis compared to control oils [122]. Interestingly, across studies, each increase in fish oil dose of 1 g/day was associated with an increase in FPG levels of approximately 3 mg/dl. A Cochrane systematic-review pooling 23 randomized controlled trials of n-3 PUFA supplementations in patients with type 2 diabetes concluded that fish oils did not result in any statistically significant increase in fasting glucose, HgbA1c, or fasting insulin, confirming no adverse effect on glycemic control [152]. Furthermore, an analysis reviewing systematically the effects of intake of n-3 PUFA on insulin sensitivity in diabetes and non-diabetes cohorts, reported no overall association [153]. However, lately, a meta-analysis suggested that higher fish and n-3 PUFA consumption may be associated with a weak increase risk of type 2 diabetes [154]; and just recently another two large analyses

pointed out differences between geographical regions in observed associations of fish consumption and risk of type 2 diabetes, with an increased risk among studies conducted in the U.S, and an inverse association between fish consumption and diabetes risk in studies conducted at Asia [155, 156]. Types of fish consumed, differences in preparation methods, and levels of contamination including selenium and mercury content, were suggested by the authors as having potential role in explaining the differences between geographical regions.

Fish Oils and Insulin Sensitivity – Mechanisms of Effects

Fish oils may decrease insulin resistance through several suggested effects. Substituting saturated fat with unsaturated fat may have beneficial effects on insulin sensitivity. In addition, the decrease in circulating triglycerides and small dense LDL particles, and the reduction of ectopic accumulation of fatty acids in muscle and liver may positively affect insulin resistance and metabolic abnormalities. Experimental studies have shown that fish oils may both reverse and prevent diet induced insulin resistance [157]. Alterations of the fatty acid composition of membrane phospholipids may modify membrane-mediated processes such as insulin transduction signals, activity of lipases and synthesis of eicosanoids, improving glucose uptake and insulin sensitivity [158, 159]. Inhibition of inflammatory pathways by fish oils are also thought to reduce insulin resistance. In addition, fish oils participate in the regulation of the expression of genes involved in adipogenesis, glucose and lipid metabolism, by modulating the activity of transcription factors such as PPARs and SREBP-1c [160]. Regarding the unclear evidence suggesting negative impact of fish oils on glycemic control, It was suggested that by decreasing triglyceride synthesis from carbohydrates, fish oils could in some individuals result in modestly increased shunting of carbohydrates and glycerol to glucose production, which may raise FPG levels, but additionally reduce hepatic steatosis and insulin resistance and thus may not adversely affect systemic metabolic function [125].

Concluding Remarks

It seems that whereas high doses of fish oils (above current guidelines recommendations) may possibly worsen to some extent glucose control, moderate intake of n-3 PUFA does not appear in clinical studies to have significant adverse effects on glucose regulation or insulin resistance, and no major harmful or beneficial associations with the development of diabetes is generally observed [160, 161]. Although experimental studies indicate that fish oils are involved in glucose control and improve insulin sensitivity, at present, in light of continuing inconclusive results of large data analyses with potential biases and confounders, it is unclear whether n-3 PUFA may have clinically relevant effects on insulin resistance or diabetes risk in humans. Nevertheless, fish oils continue to be an important part of the therapeutic arsenal for use in the treatment of severe hypertriglyceridemia and mixed dyslipidemia, which are associated with metabolic derangements and cardiovascular disease risk.

Ezetimibe

Ezetimibe is a selective inhibitor of cholesterol absorption from the intestine, lowering plasma LDL-C levels in humans by 15–20 %. The main mechanism of action includes blocking the transport protein Niemann-Pick C1-Like 1 transporter (NPC1L1) in the brush boarder of enterocytes [162]. Trials have demonstrated that ezetimibe, used as monotherapy or in combination with statins, has well-documented hypocholesterolemic effects. However, it has not yet been shown unequivocally to improve clinical outcomes of regression of atherosclerosis and reduction in cardiovascular morbidity and mortality [163].

Research studies, in particular in experimental animal models, suggest that ezetimibe may have positive effects on glycemic control. Lack of NPC1L1 or treatment with ezetimibe were shown to reduce weight gain when animals were fed a diabetogenic diet, and also conferred protection against diet-induced hyperglycemia and insulin resistance [164]. Ezetimibe treatment also improved insulin and plasma glucose response in obese fatty rats [165]. Similar results in animal studies indicate that NPC1L1 contributes to hepatic insulin resistance through cholesterol accumulation, and its inhibition could be a potential therapeutic target in the event of hepatic insulin resistance [166]. Eezetimibe was also recently been shown to improve glucose tolerance, increase insulin sensitivity, and protect the function of beta-cells in diabetic mice [167]. A suggested mechanism by which ezetimibe may ameliorate hepatic insulin resistance as well as hepatic steatosis, is via improved insulin signaling, as evidenced by the increase in Akt phosphorylation, up-regulation of SHP (small heterodimer partner), and the down-regulation of SREBP-1c expressions, in high-fat-diet–induced obese mice [168]. Studies also suggest a possible involvement of incretin GLP-1 in the ezetimibe-mediated beneficial effects on glycemic control [169, 170].

Several small human studies using monotherapy and/or combination therapies with ezetimibe also reported significant reduction in measures of insulin resistance and fatty liver [171–173]. In addition, a recent study in humans reported that treatment with ezetimibe in combination with statins resulted in a significant decrease in HgbA1c (−0.3 % from baseline, $p<0.05$) and fasting serum insulin levels, despite no

significant difference in glucose levels [174]. However, other human studies did not find significant changes in parameters of glucose metabolism and insulin sensitivity under ezetimibe therapy [175–177].

Most of the large clinical efficacy trials evaluating ezetimibe did not evaluate glucose dysregulation as part of study outcomes or adverse effects. Moreover, since a significant part of these trials were combination trials with statins, it is more difficult to assess the individual impact of ezetimibe on glucose metabolism in clinical practice. A recent pooled analysis of 27 randomized trials assessing efficacy and safety of ezetimibe/statin combination therapy was unable to investigate the effects of ezetimibe on glycemia due to limitations in studies design [178].

The current data imply that Inhibition of intestinal cholesterol absorption with ezetimibe may ameliorate glycemic control and insulin sensitivity, especially in metabolic disorders such as obesity and hepatic steatosis. However, human studies are yet small and report inconclusive results.

Cholesteryl Ester Transfer Protein (CETP) Inhibitors

In recent years, evidence from animal and clinical studies suggests that HDL affect glucose homeostasis and may have anti-diabetic properties. Infusion of reconstituted HDL has been shown to increase insulin secretion and improve glucose metabolism in subjects with diabetes mellitus [179]. Proposed mechanisms for these effects include enhanced AMP-activated protein kinase dependent uptake of glucose by skeletal muscle, modulation of insulin secretion from pancreatic beta-cells, and improvement in insulin sensitivity [179, 180].

CETP mediates the transfer of lipids between triglyceride rich lipoprotein particles and HDL. Modulation of CETP increases HDL-C levels and enhances reverse cholesterol transport, and thus could be a promising strategy to reduce residual cardiovascular risk. Several CETP inhibitors are being evaluated in phase 3 outcome clinical trials. Torcetrapib and dalcetrapib have been early terminated due to adverse effects and lack of efficacy, while anacetrapib and evacetrapib are currently under investigation in large-scale clinical outcome trials in patients with coronary artery disease.

In line with the emerging evidence implicating HDL in glucose metabolism, it was hypothesized that increasing the level of HDL by CETP inhibition may improve glycemic control and delay the onset of type 2 diabetes. Post-hoc analysis of the ILLUMINATE trial, reported that raising HDL-C levels with the CETP inhibitor torcetrapib improved glycemic control in type 2 diabetic patients [181]. Patients treated with torcetrapib in conjunction with atorvastatin had lower fasting glucose and HgbA1c (−0.33 %) at 3 months compared with those using the statin alone. This effect may have been mediated by enhanced beta-cell function. A recent animal model study supports these results, showing improvement in glucose homeostasis in dyslipidemic, insulin resistant hamsters treated with torcetrapib [182]. Additional supporting evidence comes from a study demonstrating lower levels of plasma glucose in individuals with genetic deficiency of CETP [183], and research reporting that CETP inhibition in healthy humans increases postprandial insulin and promote β-cell glucose-stimulated insulin secretion, potentially via enhanced β-cell cholesterol efflux [184].

Despite these encouraging results, it should be noted that no significant differences were seen in the rate of new-onset diabetes in clinical trials involving CETP inhibitors, including torcetrapib. Therefore, it still remains unclear whether CETP inhibition may be a promising intervention for modulation of glucose homeostasis.

Summary and Conclusions

Medications altering lipoprotein levels have pharmacological effects beyond lipid metabolism. It appears that all aforementioned lipid lowering drugs are implicated in glucose homeostasis, with some having opposing effects (Table 1). To summarize briefly, statins and nicotinic acids are associated with a modest increase in the risk of developing new-onset diabetes and impaired glucose control, while BAS have concomitant lipid and glucose lowering effects of moderate degree, and fibrates (particularly the pan-PPAR agonist bezafibrate) may produce beneficial effects on glucose metabolism and insulin sensitivity. Ezetimibe, by inhibiting intestinal cholesterol absorption, is implied to ameliorate metabolic markers such as hepatic steatosis and insulin resistance, while fish oils which are reported in experimental studies to produce favorable effects on insulin resistance, although studied extensively, continue to show inconclusive effects on glucose homeostasis in studies in patients with type 2 diabetes. HDL raising properties of CETP inhibitors may also have future therapeutic potential in the management of impaired glucose metabolism.

Even though mechanisms in some cases remain speculative, and clinical evidence may be in part inconclusive, the cumulative data on the effects of each class of lipid-lowering drugs on glucose control and diabetes risk is important for clinical practice, and should be taken into account when considering lipid-lowering therapies, especially in patients groups in which the cardiovascular benefits of lipid-lowering medications are not sufficiently proven. The need to balance between the risk of impaired glucose control and the beneficial effects on lipid profile should not deter from treating patients with existing or high cardiovascular risk, since management of dyslipidemia in these populations considerably reduce adverse cardiovascular outcomes, especially in diabetes which is considered a cardiovascular risk equivalent state. When prescribing lipid-lowering drugs which may adversely

affect glucose regulation, it is desirable to inform the patients about the potential risk, monitor blood glucose levels in treated patients especially in individuals with baseline impaired fasting glucose or clustering of metabolic risk factors, and adhere to healthy lifestyle habits that include regular exercise, weight control, and healthy food choices.

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