Role of bile acid sequestrants in the treatment of type 2 diabetes

Kohzo Takebayashi, Yoshimasa Aso, Toshihiko Inukai

Abstract
Cholestyramine is a first-generation bile acid sequestrant (BAS) and antihyperlipidemic agent that currently has limited use because of its relatively weak effect on lowering low-density-lipoprotein (LDL)-cholesterol (C) and poor tolerability. The current first choice drugs for hyper-LDL-cholesterolemia are 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors (statins) because of their strong LDL-C lowering effects and efficacy in prevention of cardiovascular disease. However, after lowering the target levels of LDL-C in very high risk patients, combination therapy with statins and other antihyperlipidemic drugs may become more important for treatment of hyper-LDL-cholesterolemia. Second-generation BASs such as colesevelam (used clinically in the USA since 2000[9-11] and colestimide (also called colestilan, and used clinically in Japan since 1999[12]) have improved tolerability. BASs also have a glucose-lowering effect[9-16], and are currently being re-evaluated for their potential use in combination with statins or antidiabetic agents.

© 2010 Baishideng. All rights reserved.

Key words: Bile acid; Bile acid sequestrant; Type 2 diabetes

Peer reviewers: Nikolaos Papanas, MD, Assistant Professor in Internal Medicine, Assistant Professor in Internal Medicine,

Democritus University of Thrace, G. Kondyli 22, Alexandroupolis 68100, Greece; Joseph Ndisang, Professor, Department of Physiology, University of Saskatchewan College of Medicine, 107 Wiggins Road, Saskatoon, Saskatchewan, S7N 5E5, Canada

Takebayashi K, Aso Y, Inukai T. Role of bile acid sequestrants in the treatment of type 2 diabetes. World J Diabetes 2010; 1(5): 146-152 Available from: URL: http://www.wjgnet.com/1948-9358/full/v1/i5/146.htm DOI: http://dx.doi.org/10.4239/wjd.v1.i5.146

INTRODUCTION
Bile acid sequestrants (BASs) were one of the first classes of drugs to show that cholesterol-lowering therapy decreases the risk of cardiovascular disease (CAD)[2,3]. However, use of first-generation BASs such as cholestyramine and colestipol has been limited by poor tolerability and a relatively weak effect on lowering of low-density lipoprotein cholesterol (LDL-C)[2-4]. Currently, 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors or statins are the first choice for treatment of hyper-LDL-cholesterolemia based on their stronger LDL-C lowering effect and prevention of cardiovascular events[1-4]. However, co-administration of BASs with statins may produce lower LDL-C levels[5,6]. Second-generation BASs such as colesevelam and colestimide have a glucose-lowering effect and improved tolerability, which has led to re-evaluation of their utility in combination with statins or antidiabetic agents.

MECHANISMS UNDERLYING THE LDL-C LOWERING EFFECT OF BILE ACID SEQUESTRANTS
Biliary excretion of cholesterol as a component of bile is
an important excretion pathway for hepatic cholesterol. Conversion of cholesterol to bile acids in the liver and excretion into the intestine via the biliary duct and gall bladder also facilitates excretion of cholesterol. Over 95% of bile acids excreted in bile from the gall bladder are reabsorbed in the terminal ileum and transferred to the liver via the portal vein in a recycling pathway. BASs, which are not themselves absorbed from the gut, absorb bile acids in the intestine and inhibit enterohepatic circulation of bile acids by preventing their reabsorption. This causes a significant increase of bile acids bound to BASs in feces. The decrease in bile acids transferred to the liver via the portal vein leads to upregulation of hepatic cholesterol cytochrome P450 7 alpha1 (CYP7A1), the rate-limiting enzyme for conversion of cholesterol to bile acids, promoting compensatory conversion and, thereby resulting in a decrease of intrahepatic cholesterol. In turn, this activates the hepatic LDL receptor, which then binds circulating LDL-C and results in a decrease in the level of circulating LDL-C[17]. BASs also inhibit cholesterol absorption by preventing formation of micelles composed of bile acids in the intestinal lumen, which may also contribute to the LDL-C lowering effect.

MECHANISMS UNDERLYING THE GLUCOSE-LOWERING EFFECT OF BILE ACID SEQUESTRANTS

Many clinical studies have shown that BASs improve glycemic control in patients with type 2 diabetes[9-16]. The mechanisms underlying this effect remain unclear, but several have been proposed. Bile acids such as cholic acid (CA) and chenodeoxycholic acid (CDCA) are natural ligands for the farnesoid X receptor (FXR)[16-19], and activation of FXR in liver may increase the production of small heterodimer partner (SHP)[20], a protein that plays a central role in lipid and glucose metabolism via regulation of various downstream molecules[21,22]. The increase in SHP due to FXR activation increases glucose metabolism by inhibiting production of phosphoenolpyruvate carboxykinase (PEPCK)[22], an enzyme associated with gluconeogenesis (although conversely FXR activation has been shown to increase PEPCk activity and glucose levels[23]). FXR activation also represses glucose levels in a diabetic rat model[24]. Bile acids can also increase glucose metabolism by regulating energy homeostasis via activation of the G protein-coupled receptor 5 (TGR5)-cAMP-type 2 iodothyronine deiodinase (D2) pathway in brown adipose tissues or skeletal muscles independently of FXR[25]. These observations suggest that BASs might worsen glycemic control because of potential deactivation of hepatic FXR through a decrease of bile acids in liver, in contrast to the established beneficial effects of BASs for glucose metabolism. However, there is a report showing that BAS treatment does not change the level of total bile acids in serum, but increases the absolute level of CA as well as the CA level relative to total bile acids[26]. The relative increase in circulating CA may itself influence glucose metabolism through a decrease of glucose levels via the TGR5-cAMP-D2 pathway. However, even if this mechanism occurs it is unlikely to improve overall glycemic control because the level of CDCA relative to total bile acids may be decreased by BAS treatment, and CDCA has similar effects on TGR5 to those of CA[27].

The most plausible mechanism for the glucose-lowering effect of BASs may be associated with effects on the liver X receptor (LXR), as proposed by Bay et al[27]. LXR is a nuclear transcription factor that mainly regulates lipid metabolism, and its natural ligands are oxysterols such as 22(R)-hydroxycholesterol, 24(S)-hydroxycholesterol, and 27-hydroxycholesterol[28,29]. Reduction of bile acid flux in the portal vein by BAS treatment decreases FXR activity in liver, and this decreased FXR activity may induce an increase of LXR activity due to decreased SHP production[30]. LXR activation in liver results in improved glucose sensitivity by preventing gluconeogenesis based on inhibition of the activity of PEPCK and G6Pase[30]. LXR activation may also improve glucose metabolism by promoting expression of glucokinase and glucose transporter 4 (GLUT4) in adipocytes[31] or by promoting insulin secretion in β cells in the pancreas[32]. However, LXR activation may simultaneously increase circulating triglyceride levels by promoting production of stimulating sterol regulatory element-binding protein 1c (SREBP1c) in liver[33]. On the other hand, decreased FXR activity in liver may itself promote PEPCK or SREBP1c production via reduction of SHP[16,22]. Therefore, FXR deactivation and resulting LXR activation may have competitive effects on molecules such as PEPCK. However, it is likely that regulation of glucose or lipid metabolism by FXR activation probably overcomes the effects of FXR deactivation[34]. These mechanisms suggest that in liver both activation of FXR by FXR agonists such as CA and CDCA, and deactivation of FXR by BASs improve glycemic control, although these changes have opposite effects on TG production via SREBP1c (decreased by FXR agonists and increased by BASs).

BAS-induced secretion of glucagon-like peptide-1 (GLP-1) in the ileum may be another important mechanism. Bile acids can increase GLP-1 secretion in L cells in the intestine via TGR5[19]. However, a recent report[35] showed that colesevelam also induced the release of GLP-1 and improved plasma glucose levels and insulin resistance in the diet-induced obesity (F-DIO) rat fed a high fat/high sucrose (HF) diet. In contrast, administration of SC-435, an inhibitor of the apical sodium-dependent bile acid transporter (ASBT), did not change GLP-1, glucose levels, and insulin sensitivity in F-DIO rats fed the HF diet, compared to untreated F-DIO rats fed the same diet[36]. Addition of both colesevelam and SC-435 reduced the total concentration of bile acids in portal blood and increased CYP7A1 mRNA expression in liver, which reflects FXR deactivation[35]. These findings suggest that colesevelam can improve glycemic control by increasing GLP-1 levels in the circulation independently of an
Circulating GLP-1 FXR activity in liver

November 15, 2010

LDL-C levels by 13% and 28%, respectively, compared activity in liver, which leads to increased small heterodimer partner (SHP) production that inhibits phosphoenolpyruvate carboxykinase (PEPCK) and therefore inhibits significantly decreased HbA1c with sulfonylurea or metformin, alone or in combination patients with type 2 diabetes that was not fully controlled showed that addition of colesevelam at 3.75 g/d in 65 pilot study of the effect of colesevelam on glucose levels decreasing effect of second-generation BASs such as colesevelam decreased postprandial plasma glucose levels, but increased GLP-1 in patients with type 2 diabetes It is clear that the mechanisms underlying the glucose-lowering effect of BASs are complicated and other mechanisms may also be involved. The possible mechanisms are summarized in Figure 1.

**EFFECTS OF BAS ON GLUCOSE AND LIPID METABOLISM IN PATIENTS WITH TYPE 2 DIABETES**

The glucose-lowering effect of first-generation BASs such as cholestyramine was shown in the 1990s, but there was little subsequent interest in this effect for several years. In a small randomized, double-blind, crossover trial in 21 patients (20 men and 1 woman) with type 2 diabetes complicated with dyslipidemia treated with glibenclamide or insulin, cholestyramine administered at 16 g/d for 6 months significantly decreased the mean plasma glucose and LDL-C levels by 13% and 28%, respectively, compared with placebo. A decrease of glycated hemoglobin from 8.8% to 8.3% (not significant) also occurred. The glucose-lowering effect of second-generation BASs such as colesevelam and colestimide has attracted more attention. In a 26 wk study in 461 patients with type 2 diabetes treated with sulfonylurea as monotherapy or in combination with other oral antidiabetes drugs, colesevelam (3.75 g/d) significantly reduced HbA1c (baseline 8.2%) by 0.54% in all patients and by 0.79% in a subgroup treated with sulfonylurea monotherapy, and reduced fasting plasma glucose (FPG) by 13.5 mg/dL in all patients, compared with placebo. Based on the positive results for glycemic control in the GLOWS study, three phase III randomized, double-blind placebo-controlled trials with a 2 wk single blind placebo run-in were performed, in which colesevelam was added to sulfonylurea-, metformin-, and insulin-based therapy, respectively.

In a 26 wk study in 461 patients with type 2 diabetes treated with sulfonylurea as monotherapy or in combination with other oral antidiabetes drugs, colesevelam (3.75 g/d) significantly reduced HbA1c (baseline 8.2%) by 0.54% in all patients and by 0.79% in a subgroup treated with sulfonylurea monotherapy, and reduced fasting plasma glucose (FPG) by 13.5 mg/dL in all patients, compared with placebo. The reduction of HbA1c in a subgroup with HbA1c > 8.0% at baseline was 0.58% vs placebo. Colesevelam also significantly reduced LDL-C by 16.7% compared with placebo, while an insignificant elevation of HDL-C (+0.1%) and a significant elevation of triglyceride (TG) (+17.7%) were observed. In a 26 wk study in 316 patients with type 2 diabetes treated with metformin as monotherapy or in combination with other antidiabetes drugs, colesevelam (3.75 g/d) significantly decreased HbA1c (baseline 8.2%) by 0.54% in all patients and by 0.47% in a subgroup treated with metformin monotherapy, and reduced FPG by 13.9 mg/dL in all patients, compared with placebo. The reduction of HbA1c in a subgroup with HbA1c > 8.0% at baseline was 0.60% vs placebo. LDL-C was significantly reduced by 15.7%, with insignificant increases in HDL-C (+0.9%) and TG (+4.7%). In a 16 wk study in 287 patients with type 2 diabetes treated with insulin as monotherapy or in combination with other antidiabetes drugs, colesevelam (3.75 g/d) significantly decreased HbA1c (baseline 8.3%)


Takebayashi K et al: Bile acid sequestrants and type 2 diabetes

Table 1  Studies showing glucose-lowering effect of bile acid sequestrants

| n  | Duration (wk) | Therapy          | Baseline (g/d) | Hba1c (%) | ΔHba1c | ΔLDL-C | Others                  |
|----|---------------|------------------|----------------|-----------|--------|--------|-------------------------|
| 21 | 6             | cholestyramine   | 16.00          | no description | -0.50% | -28.00% |                         |
| 65 | 12            | colesevelam      | 3.75           | 7.90%     | -0.50% | -11.70% |                         |
| 461| 26            | colesevelam      | 3.75           | 8.20%     | -0.54% | -16.70% | ΔCRP-11.2%              |
| 316| 26            | colesevelam      | 3.75           | 8.20%     | -0.54% | -15.90% | ΔCRP-14.4%              |
| 287| 16            | colesevelam      | 3.00           | 8.30%     | -0.50% | -12.80% | ΔCRP-12.2%              |
| 70 | 12            | colestimide      | 3.00           | 7.70%     | -0.90% | -23.00% |                         |
| 40 | 12            | colestimide      | 3.00           | 7.90%     | -0.50% | -14.00% | Δ8-isoPGFα-32%          |
| 183| 12            | colestimide      | 4.50           | 8.00%     | -0.90% | -22.50% |                         |

ΔHbA1c (change of hemoglobin A1c) is shown as the difference between BAS and placebo except for b. Glycated hemoglobin. aChange from baseline. ΔLDL-C: change of low-density-lipoprotein cholesterol; ΔCRP: change of C reactive protein by treatment (statistical significance); Δ8-isoPGFα: change of urinary 8-iso-prostaglandin F2α (a marker of systemic oxidative stress) by treatment (statistical significance).

by 0.5% in all patients and by 0.59% in a subgroup treated with insulin monotherapy, compared with placebo\[16\]. The reduction of HbA1c in a subgroup with HbA1c > 8.0% at baseline was 0.57% vs placebo, with an insignificant reduction of FPG (-14.6%). LDL-C was significantly reduced (-12.8%), TG was significantly increased (+21.5%), and HDL-C showed a small and insignificant decrease (-0.9%).

The mean percent compliance in the three studies with sulfonylurea, metformin, and insulin was high: 93.3%, 92.3%, and 92.7% in the colesevelam group, with similar rates in the placebo group. The results of these studies suggest that colesevelam can reduce HbA1c levels by approximately 0.5% in all type 2 diabetic patients when added to sulfonylurea, metformin, or insulin-based therapy. The effect on glycemic control of colesevelam as monotherapy or in combination with other antidiabetes drugs in patients with type 2 diabetes is less clear. However, given the possible effect of BASs on GLP-1, as described above, it will be interesting to investigate the effect of coadministration of colesevelam with a dipeptidyl peptidase IV (DPPIV) inhibitor, which improves glycemic control by preventing degradation of circulating GLP-1.

An effect of colestimide on glycemic control in patients with type 2 diabetes has also been reported. Yamakawa et al randomly assigned patients with type 2 diabetes complicated by hyperlipidemia to colestimide (3.0 g/d) or pravastatin (10 mg/d) treatment groups, and investigated the effect of these drugs on lipid and glucose metabolism\[15\]. In both groups, 33 of 35 patients received monotherapy with oral antidiabetic drugs or insulin, or combination therapy with these agents. Colestimide and pravastatin significantly decreased LDL-C levels by 23% and 17%, respectively, but only colestimide produced a significant decrease in HbA1c (0.9% reduction from a baseline level of 7.7%) after 3 mo of therapy. In our study of colestimide (3.0 g/d; n = 20) compared to rosuvastatin (2.5 mg/d; n = 20) in patients with type 2 diabetes complicated with hyper-LDL-cholesterolemia, HbA1c decreased by approximately 0.6% from a baseline level of 7.9%, with a treatment difference of 0.5% between colestimide and rosuvastatin after treatment for 3 mo\[16\]. LDL-C was decreased by rosuvastatin and colestimide by 39% and 14%, respectively. All except 3 patients in the colestimide group had already taken other antidiabetic drugs. Kondo and Kadokawa also recently reported an effect of high dose colestimide therapy (4.5 g/d) on glycemic control in a randomized double-blind placebo-controlled study (n = 183 at the start of randomization)\[12\]. Colestimide was generally administered as monotherapy, except in a few patients. After 3 mo, a 0.9% reduction of HbA1c and a decrease in FPG of 22 mg/dL were observed in the colestimide group (n = 86) compared with the placebo group (n = 86). In subgroups of patients with HbA1c 8.0 to < 9.0% and ≥ 9.0%, colestimide decreased HbA1c by 1.0% and 1.5%, respectively, compared to placebo. Based on these reports, the HbA1c-lowering effect of colestimide appears to be somewhat stronger than that of colesevelam. It is important to note that the colestimide trials were all performed in Japan, and that the clinical characteristics of the patients differed from those in trials of colesevelam. A trial with direct comparison of the effects of colesevelam and colestimide on glycemic control has yet to be performed. Co-administration of colestimide with DPPIV inhibitors has also not been studied. Studies showing glucose-lowering effect of bile acid sequestrants are summarized in Table 1.

**SAFETY, TOLERABILITY, AND DRUG INTERACTIONS IN BAS TREATMENT**

As mentioned above, cholestyramine, a first-generation BAS, was shown to lower LDL-C before the clinical use of statins, and was one of the first drugs to show that lowering cholesterol could decrease the risk of CAD\[37\]. However, after the appearance of statins, use of cholestyramine has been limited because of its relatively weak LDL-C lowering effect compared with statins, and because of poor compliance due to a high frequency of side effects, high dosage, requirement for suspension in water, and unpleasant taste\[37\]. Colestipol, another first-generation BAS, was better tolerated by patients than cholestyramine, but its effects were still not satisfactory\[37\]. The main side effect of BASs is gastrointestinal symptoms including dyspepsia, nausea, and particularly constipation, while systemic severe side effects are rare. Regarding the mechanism of constipation induced by BAS, CDCA in feces promotes secretion of water and electrolytes into...
the intestine by activating adenyl cyclase and increasing intracellular cAMP in colonic mucosa cells\(^{[38,39]}\). BAS absorbs bile acids, which causes a decrease in the level of intracellular bile acids and this may induce constipation.

Colesevelam and colestimide are second-generation BASs with reduced side effects, including constipation. For WelChol\(^\text{®}\) (colesevelam hydrochloride)\(^{[38]}\), the frequency of adverse reactions is relatively low, with 11.0%\(^\text{a}\), 8.3%\(^\text{a}\), and 4.2% of patients developing constipation, dyspepsia, and nausea, respectively, compared to 7.0%\(^\text{a}\), 3.5%\(^\text{a}\), and 3.9%\(^\text{a}\), respectively, with placebo. Myalgia was found in 2.1% of patients treated with colesevelam compared to 0.4% with placebo. The frequency of constipation with colestimide has been reported to be 3.6%\(^{[31]}\). Both colesevelam and colestimide can be administered as tablets (the latter is also formulated as a granulated powder). The tablet size is still somewhat large, but the drug compliance is better than that for cholestyramine. In addition, BASs can be used safely in children, in pregnant women, and in patients with liver and renal disease because they are not absorbed systemically.

Drug interactions are also an important concern in BAS administration. Cholestyramine has many drug interactions since it increases the absorption of common drugs including digoxin, diuretics, estrogens, hydrocortisone, propranolol, thyrxine, and warfarin, and may also interfere with fat-soluble vitamins such as vitamins A, D, E and K\(^{[3]}\). Therefore, it is recommended that other drugs are taken at least 1 h before or 4 h after cholestyramine treatment. In contrast, colesevelam does not influence the bioavailability of digoxin, fenofibrate, lovastatin, metoprolol, quinidine, valproic acid, pioglitazone, and warfarin\(^{[3]}\). Drugs with a known interaction with colesevelam include glyburide, levethoxyamine, and oral contraceptives containing ethinyl estradiol and norethindrone, and it is recommended that these drugs should be taken at least 1 hour prior to colesevelam administration\(^{[196]}\). In summary, severe side effects of BASs are rare, and second-generation BASs have improved tolerability and reduced drug interactions compared to first-generation BASs.

**BASS IN THE TREATMENT OF TYPE 2 DIABETES: CURRENT ROLE AND FUTURE PERSPECTIVES**

The main role of BASs in treatment of diabetes appears to be as second-line drugs in combination with other antidiabetic agents. The glucose-lowering effect of BASs is moderate to mild, and BAS monotherapy for diabetes has only been examined in one study of colestimide\(^{[12]}\). In fact, colesevelam is only currently approved as adjunct therapy for glycemic control in type 2 diabetes in the USA (since 2008), and colestimide has yet to be approved for treatment of type 2 diabetes alone. As discussed above, BASs can decrease HbA\(_1\)c by 0.5% to 0.9%\(^{[10]}\), and the glucose-lowering effect of BASs may be stronger in patients with higher baseline HbA\(_1\)c levels\(^{[9,12,14,16]}\). BASs rarely cause body weight gain or increase hypoglycemia\(^{[9,11]}\), and second-generation BASs have improved drug compliance due to reduced side effects of constipation or dyspepsia\(^{[9,11,40]}\). Systemic severe side effects of BASs are rare. These characteristics support the utility of BASs as additional drugs for treatment of diabetes.

It is apparent that BASs are more suitable for treatment of patients with type 2 diabetes complicated with hyper-LDL-cholesterolemia, rather than patients with type 2 diabetes alone, because there is evidence that reduction of LDL-C by cholestyramine decreases the risk of CAD\(^{[112]}\). However, statins are now established as the first choice treatment for hyper-LDL-cholesterolemia due to their strong LDL-C lowering effect and prevention of cardiovascular events\(^{[44]}\). The beneficial effect of rosuvastatin for prevention of cardiovascular events even extends to apparently healthy men and women with baseline LDL-C levels < 130 mg/dL, but high-sensitivity C reactive protein (CRP) of ≥ 2 mg/L\(^{[41]}\). A beneficial effect of atorvastatin for prevention of cardiovascular events has also been shown in patients with type 2 diabetes with relatively low LDL-C levels (≤ 160 mg/dL)\(^{[42]}\).

The target LDL-C level in very high-risk patients (those with cardiovascular disease with diabetes, cigarette smoking or factors associated with metabolic syndrome) has recently been lowered to ≤ 70 mg/dL\(^{[44]}\). This suggests that combination therapy will become more important in patients who cannot achieve the target levels, even with high dose statins, or cannot tolerate high dose statins because of side effects such as myalgia. In addition, a recent meta-analysis suggested that most statins, including rosuvastatin and atorvastatin, are weakly but significantly associated with new onset of type 2 diabetes\(^{[46]}\). This potentially deleterious effect of statins on glucose metabolism may become more apparent when they are used at a high dose\(^{[46]}\). Therefore, combination therapy of statins with other anti-hyperlipidemic drugs may be appropriate, and addition of BASs to statin therapy may be suitable, especially for type 2 diabetes with hyper-LDL-cholesterolemia. It should be noted that it is still unclear whether statins worsen glycemic control after onset of type 2 diabetes. Regarding the effects of BASs, colesevelam monotherapy can decrease LDL-C by 15% to 21%\(^{[37,40,45,46]}\) and by a further 10% in combination with statins\(^{[48]}\). However, care is required with use of BASs in patients with high TG levels because of a potential TG elevation effect\(^{[15]}\). Anti-inflammatory and anti-oxidative stress effects of BASs have also been reported in patients with type 2 diabetes\(^{[8,16]}\).

The above findings suggest that BASs are especially suitable for patients with type 2 diabetes complicated by hyper-LDL-cholesterolemia, since these patients often fail to achieve target levels of HbA\(_1\)c and LDL-C with use of other antidiabetes drugs and statins. However, there is still no evidence to show that addition of second-generation BAS such as colesevelam and colestimide reduces the risk of cardiovascular events in these patients.

**CONCLUSION**

Second-generation BASs such as colesevelam and coles-
timid are generally well tolerated and severe systemic side effects are rare. When BAS is coadministered with antidiabetes drugs such as sulfonylurea, metformin and insulin, a reduction in HbA1c of approximately 0.5% to 0.9% can be expected without increased hypoglycemia or weight gain. The LDL-C lowering effect of BASs is relatively mild, but coadministration of a BAS with statins is likely to produce a further decrease of LDL-C.

**REFERENCES**

1. The Lipid Research Clinics Coronary Primary Prevention Trial results. I. Reduction in incidence of coronary heart dis-
ease. JAMA 1984; 251: 351-364

2. Lipid Research Clinics Program: The Lipid Research Clinics Coronary Primary Prevention Trial Results. II. The relationship of reduction in incidence of coronary heart disease to cholesterol lowering. JAMA 1984; 251: 365-374

3. Randomised trial of cholesterol lowering in 4444 patients with coronary heart disease: the Scandinavian Simvastatin Survival Study (4S). Lancet 1994; 344: 1383-1389

4. Colhoun HM, Betteridge DJ, Durrington PN, Hitman GA, Neil HA. The management of hyperlipidaemia in patients with diabetes. BMJ 2008; 336: 746-752

5. Ridker PM, Danielson E, Fonseca FA, Genest J, Goto AM Jr, Kastelein JJ, Kissela BM, Koenig W, Libby P, Lorenzatti AJ, MacFadyen JG, Moncada S, Mohler ER, Mora S, Murphy PL, O’Donnell CJ, Pratley RE, Ridker PM, Sacks FM, Shaw LJ, Smith SC Jr, 31. 2005; 361: 1267-1278

6. Hunninghake D, Insull W Jr, Toth P, Davidson D, Donovan JM, Burke SK. Coadministration of colesevelam hydrochloride with atorvastatin lowers LDL-C additively. Atherosclerosis 2001; 158: 407-416

7. Bays HE, Davidson M, Jones MR, Abby SL. Effects of colesevelam hydrochloride on low-density lipoprotein cholesterol and high-sensitivity C-reactive protein when added to statins in patients with hypercholesterolemia. Ann Intern Med 2006; 145: 1198-1205

8. Fonseca VA, Rosenstock J, Wang AC, Truitt KE, Jones MR. Colesevelam HCl improves glycemic control and reduces LDL cholesterol in patients with inadequately controlled type 2 diabetes on sulfonylurea-based therapy. Diabetes Care 2008; 31: 1479-1484

9. Bays HE, Goldberg RB, Truitt KE, Jones MR. Colesevelam hydrochloride therapy in patients with type 2 diabetes mellitus treated with metformin: plasma, glucose and lipid effects. Arch Intern Med 2008; 168: 1975-1983

10. Goldberg RB, Fonseca VA, Truitt KE, Jones MR. Efficacy and safety of colesevelam in patients with type 2 diabetes mellitus and inadequate glycemic control receiving insulin-based therapy. Arch Intern Med 2008; 168: 1531-1540

11. Kondo K, Kodawati T. Colestilan monotherapy significantly improves glycaemic control and LDL cholesterol levels in patients with type 2 diabetes: a randomized double-blind placebo-controlled study. Diabetes Obes Metab 2010; 12: 246-251

12. Garg A, Grundy SM. Cholestyramine therapy for dyslipidemia in non-insulin-dependent diabetes mellitus. A short-term, double-blind, crossover trial. Ann Intern Med 1994; 121: 416-422

13. Zieve FJ, Kalin MF, Schwartz SL, Jones MR, Bailey WL. Results of the glucose-lowering effect of WelChol study (GL-OWS): a randomized, double-blind, placebo-controlled pilot study evaluating the effect of colesvelam hydrochloride on glycemic control in subjects with type 2 diabetes. Clin Ther 2007; 29: 74-83

14. Yamakawa T, Takano T, Utsunomiya H, Kadonosono K, Okamura A. Effect of colestimate therapy for glycemic control in type 2 diabetes mellitus with hypercholesterolemia. Endocr J 2007; 54: 53-58

15. Takebayashi K, Suetsumu S, Matsumoto S, Aso Y, Imukai T. Effects of rosuvastatin and colestimate on metabolic parameters and urinary monocyte chemoattractant protein-1 in type 2 diabetic patients with hyperlipidemia. South Med J 2009; 102: 361-368

16. Bays H, Dujovne C. Colesevelam HCl: a non-systemic lipid-lowering drug. Expert Opin Pharmacother 2003; 4: 779-790

17. Staels B, Kuipers F. Bile acid sequestrants and the treatment of type 2 diabetes mellitus. Drugs 2007; 67: 1383-1392

18. Lefebvre P, Cariou B, Lien F, Kuipers F, Staels B. Role of bile acids and bile acid receptors in metabolic regulation. Physiol Rev 2009; 89: 147-191

19. Brendel C, Schoonjans K, Botrugno OA, Treuher T, Auwerx J. The small heterodimer partner interacts with the liver X receptor alpha and represses its transcriptional activity. Mol Endocrinol 2002; 16: 2065-2076

20. Watanabe M, Houten SM, Wang L, Moschetta A, Mangelsdorf DJ, Heyman RA, Moore DD, Auwerx J. Bile acids lower triglyceride levels via a pathway involving FXR, SHP, and SHREW-1c. J Clin Invest 2004; 113: 1408-1418

21. Ma K, Saha PK, Chan L, Moore DD. Farnesoid X receptor is essential for normal glucose homeostasis. J Clin Invest 2006; 116: 1102-1109

22. Stayrook RK, Brannleit KS, Savkur RS, Ficorilli J, Cook T, Chrisite ME, Michael LF, Burris TP. Regulation of carbohydrate metabolism by the farnesoid X receptor. Endocrinology 2005; 146: 984-991

23. Zhang Y, Lee FY, Barrera G, Lee H, Vales C, Gonzalez FJ, Willson TM, Edwards PA. Activation of the nuclear receptor FXR improves hyperglycemia and hyperlipidemia in diabetic mice. Proc Natl Acad Sci USA 2006; 103: 1006-1011

24. Watanabe M, Houten SM, Matak bricks and bile acid receptors in metabolic regulation. Proc Natl Acad Sci USA 2006; 103: 1006-1011

25. Stayrook RK, Bramblett KS, Savkur RS, Ficorilli J, Cook T, Christie ME, Michael LF, Burris TP. Regulation of carbohydrate metabolism by the farnesoid X receptor. Endocrinology 2005; 146: 984-991

26. Saha PK, Chan L, Moore DD. Farnesoid X receptor is essential for normal glucose homeostasis. J Clin Invest 2006; 116: 1102-1109

27. Stayrook RK, Bramblett KS, Savkur RS, Ficorilli J, Cook T, Christie ME, Michael LF, Burris TP. Regulation of carbohydrate metabolism by the farnesoid X receptor. Endocrinology 2005; 146: 984-991

28. Saha PK, Chan L, Moore DD. Farnesoid X receptor is essential for normal glucose homeostasis. J Clin Invest 2006; 116: 1102-1109

29. Stayrook RK, Bramblett KS, Savkur RS, Ficorilli J, Cook T, Christie ME, Michael LF, Burris TP. Regulation of carbohydrate metabolism by the farnesoid X receptor. Endocrinology 2005; 146: 984-991

30. Saha PK, Chan L, Moore DD. Farnesoid X receptor is essential for normal glucose homeostasis. J Clin Invest 2006; 116: 1102-1109

31. Stayrook RK, Bramblett KS, Savkur RS, Ficorilli J, Cook T, Christie ME, Michael LF, Burris TP. Regulation of carbohydrate metabolism by the farnesoid X receptor. Endocrinology 2005; 146: 984-991

32. Saha PK, Chan L, Moore DD. Farnesoid X receptor is essential for normal glucose homeostasis. J Clin Invest 2006; 116: 1102-1109

33. Stayrook RK, Bramblett KS, Savkur RS, Ficorilli J, Cook T, Christie ME, Michael LF, Burris TP. Regulation of carbohydrate metabolism by the farnesoid X receptor. Endocrinology 2005; 146: 984-991

34. Saha PK, Chan L, Moore DD. Farnesoid X receptor is essential for normal glucose homeostasis. J Clin Invest 2006; 116: 1102-1109
 agonist mediated by inhibition of hepatic gluconeogenesis. *J Biol Chem* 2003; 278: 1131-1136

31 Laffitte BA, Chao LC, Li J, Walczak R, Hummasti S, Joseph SB, Castrillo A, Wilpitz DC, Mangelsdorf DJ, Collins JL, Saet E, Tontonoz P. Activation of liver X receptor improves glucose tolerance through coordinate regulation of glucose metabolism in liver and adipose tissue. *Proc Natl Acad Sci USA* 2003; 100: 5419-5424

32 Efanov AM, Sewing S, Bokvist K, Gromada J. Liver X receptor activation stimulates insulin secretion via modulation of glucose and lipid metabolism in pancreatic beta-cells. *Diabetes* 2004; 53 Suppl 3: S75-S78

33 Rader DJ. Liver X receptor and farnesoid X receptor as therapeutic targets. *Am J Cardiol* 2007; 100: n15-n19

34 Gupta S, Pandak WM, Hylemon PB. LXR alpha is the dominant regulator of CYP7A1 transcription. *Biochem Biophys Res Commun* 2002; 293: 338-343

35 Shang Q, Saumoy M, Holst JJ, Salen G, Xu G. Colesevelam improves insulin resistance in a diet-induced obesity (F-DIO) rat model by increasing the release of GLP-1. *Am J Physiol Gastrointest Liver Physiol* 2010; 298: G419-G424

36 Suzuki T, Oka B, Igaru Y, Matsumura N, Watanabe K, Futami-Suda S, Yasu H, Ouchi M, Suzuki K, Kigawa Y, Nakano H. Colestipol lowers plasma glucose levels and increases plasma glucagon-like PEPTIDE-1 (7-36) levels in patients with type 2 diabetes mellitus complicated by hypercholesterolemia. *J Nippon Med Sch* 2007; 74: 338-343

37 Heel RC, Brogden RN, Pakes GE, Speight TM, Avery GS. Colestipol: a review of its pharmacological properties and therapeutic efficacy in patients with hypercholesterolaemia. *Drugs* 1980; 19: 161-180

38 Mitchell WD, Findlay JM, Prescott RJ, Eastwood MA, Horn DB. Bile acids in the diarrhoea of ileal resection. *Gut* 1973; 14: 248-253

39 Corazza GR, Ciccarelli R, Caciagli F, Gasbarrini G. Cyclic AMP and cyclic GMP levels in human colonic mucosa before and during chenodeoxycholic acid therapy. *Gut* 1979; 20: 489-492

40 WelChol® product information 2007. Colesevelam hydrochloride. Available from: URL: http://www.welchol.com/pdfs/fullPI.pdf

41 Hata M, Uchiyama K, Kajiura T, Ishibashi A. Postmarketing prospective cohort study of a cholesterol lowering drug, colestipol preparations, Cholebline®. *J New Rem Clin* 2008; 57: 754-773

42 Grundy SM, Cleeman JJ, Merz CN, Brewer HB Jr, Clark LT, Hunninghake DB, Pasternak RC, Smith SC Jr, Stone NJ. Implications of recent clinical trials for the National Cholesterol Education Program Adult Treatment Panel III guidelines. *Circulation* 2004; 110: 227-239

43 Coleman CI, Reinhart K, Kluger J, White CM. The effect of statins on the development of new-onset type 2 diabetes: a meta-analysis of randomized controlled trials. *Curr Med Res Opin* 2008; 24: 1359-1362

44 Koh KK, Quon MJ, Han SH, Lee Y, Kim SJ, Shin EK. Atorvastatin causes insulin resistance and increases ambient glycemia in hypercholesterolemic patients. *J Am Coll Cardiol* 2010; 55: 1209-1216

45 Insull W Jr, Toth P, Mullican W, Hunninghake D, Burke S, Donovan JM, Davidson MH. Effectiveness of colesevelam hydrochloride in decreasing LDL cholesterol in patients with primary hypercholesterolemia: a 24-week randomized controlled trial. *Mayo Clin Proc* 2001; 76: 971-982

46 Davidson MH, Dillon MA, Gordon B, Jones P, Samuels J, Weiss S, Isaacsohn J, Toth P, Burke SK. Colesevelam hydrochloride (cholestagel): a new, potent bile acid sequestrant associated with a low incidence of gastrointestinal side effects. *Arch Intern Med* 1999; 159: 1893-1900

47 Sonnett TE, Levyen TL, Neumiller JJ, Gates BJ, Setter SM. Colesevelam hydrochloride for the treatment of type 2 diabetes mellitus. *Clin Ther* 2009; 31: 245-259