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REVIEW

Current and Emerging Therapies in Hypercholesterolemia: Focus on Colesevelam

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Abstract

Background: Statins are recommended as first line therapy for the prevention of cardiovascular disease. Some individuals are statin intolerant or may need additional cholesterol lowering to achieve their cholesterol targets.

Purpose: To review the pharmacology, clinical efficacy and safety of colesevelam mono- and combination therapy in patients with hypercholesterolemia.

Data Source: English-language journals from PUBMED MEDLINE (without restriction of date) using key word colesevelam.

Results: Trials of colesevelam as monotherpy or in combination had baseline LDL-c levels of 130 to 202 mg/dl and triglycerides levels of 114 to 230 mg/dl. Colesevelam monotherapy reduced LDL-c by 9%–20% while increasing triglycerides 6%–25%. When added to low or moderate dose statin therapy, colesevelam decreased LDL-c an additional 6%–16%; when added to fenofibrate, colesevelam additionally decreased LDL-c by 17% and non-HDL-c by 7%; and when added to statin + niacin 2 gr additionally decreased LDL-c by 10%. The hypertriglyceridemia observed with colesevelam monotherapy was largely attenuated when colesevelam was coadministered with statins, fenofibrate, or niacin 2 gr. Coadministration of colesevelam with ezetimibe provided variable additional LDL-c reductions ranging from 0 to 20% over ezetimibe alone, and triglyceride responses were similarly variable. In diabetic individuals with modest hypertriglyceridemia, colesevelam reduced hemoglobin A1c by 0.5%. Colesevelam has fewer drug interactions than older bile acid sequestrants and is well-tolerated when used in combination with other lipid-lowering medications as well as with oral anti-diabetes medications or insulin.

Conclusion: Colesevelam is an option for patients who have not achieved their LDL-c and non-HDL-c goals with statin therapy, or who are statin intolerant. Colesevelam is also an option to lower both LDL-c and glucose levels in patients with inadequately controlled diabetes.

Keywords: colesevelam, LDL-c, hypercholesterolemia, diabetes mellitus

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Introduction

Cardiovascular disease (CVD) affects 80 million Americans (36%), and is the leading cause of death not just in the U.S. but also globally.[1,2] Reduction of low-density lipoprotein cholesterol (LDL-c) has been shown to reduce cardiovascular events in numerous primary and secondary prevention populations, and as a result LDL-c is the primary target of lipid therapy.[3] First-line pharmacological treatment for LDL-c reduction is the use of 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors (statins).[4] Even at the highest statin doses a significant percentage of patients do not achieve target LDL-c levels <100 mg/dl, and few achieve the more aggressive optional LDL-c goal <70 mg/dl.[4–6] Moreover, individuals may not be able to achieve target LDL-c levels due to statin intolerance or physician concern for potential adverse events at higher statin doses.[7] The efficacy of statin monotherapy may also be limited due the mechanism of action, since only the liver production of LDL-c is inhibited but recirculation of biliary cholesterol and absorption of dietary cholesterol are not.[8]

For these reasons, combination lipid-lowering therapy has been suggested to achieve additive lipid-lowering effect and employ the different mechanisms of action of other lipid-lowering agents.[9] The American Heart Association/American College of Cardiology guidelines for the secondary prevention of coronary heart disease have suggested the use of combination therapy of statin with either ezetimibe, bile acid sequestrant, or niacin to achieve the lower LDL-c targets.[10] Ezetimibe coadministered with a statin lowers LDL-c levels by a further 14% to achieve 25%–60% LDL-c reductions from baseline.[11] Niacin 2 grams added to a statin will lower LDL-c an additional 1% to 8%, while fibrates have minimal LDL-c lowering effects.[12–16] Bile acid sequestrants (BAS) reduce LDL-c by additional 7%–20% when added to statin therapy.[17,18] BAS lower LDL-c by inhibiting intestinal bile acid reabsorption, leading to an interruption in the enterohepatic bile acid circulation. Colesevelam is the newest BAS with an improved tolerability profile. This paper reviews colesevelam's pharmacology, efficacy and safety based on a search English-language journals from PUBMED MEDLINE (without restriction of date) using key word colesevelam.

Dosing and indications for use

The standard dose is six 625 mg tablets once daily or 3 tablets twice daily taken with a meal and liquid, for a total of 3.8 grams per day.[18] Colesevelam can be administered concurrently with a statin, ezetimibe or fenofibrate. Colesevelam is known to interfere with the absorption of glyburide, levothyroxine, and oral contraceptives and these drugs should be administered at least 4 hours prior to colesevelam. Drugs not tested for an interaction with colesevalam, such as those with a narrow therapeutic window such as phenytoin should also be administered at least 4 hours prior to colesevelam. Colesevelam is a pregnancy category B medication and compatible with lactation. It has negligible absorption and is unlikely to be affected by hepatic or renal impairment.

Colesevelam is indicated for the treatment of hypercholesterolemia in adults as monotherapy or in combination with a statin, and to improve diabetes control in adults with type II diabetes.[18] It is also approved for use in boys and postmenarchal girls, 10 to 17 years of age, with heterozygous familial hypercholesterolemia (heFH) alone or in combination with a statin after failing an adequate trial of diet therapy.

Mechanism of Action, Metabolism and Pharmacokinetic Profile

Colesevelam hydrochloride is a non-absorbed polymer (water-absorbing hydrogel) engineered to bind bile acids.[19] It consists of a polyallylamine cross-linked with epichlorohydrin and alkylated with 1-bromodecane and 6-bromo-hexyltrimethylammonium bromide.

Mechanism of action

Bile provides about two-thirds of daily cholesterol (800–1200 mg) in the intraluminal pool, while the diet provides 300–500 mg cholesterol and intestinal sloughing 300 mg.[20] Bile acids are synthesized from hepatic cholesterol and stored in the gallbladder, from which they are secreted into the small intestine to solubilize dietary fats to enhance absorption.[21] Bile acids are 95% reabsorbed from the distal ileum and transported back to the liver via the enterohepatic circulation. In addition to stimulating absorption of cholesterol, fat soluble vitamins and lipids from the intestine, bile acids are active regulatory molecules. Bile acids activate specific nuclear receptors (farnesoid X (FXR), pregnane X receptor, and vitamin D

receptor), G coupled receptor TGR5, and cell signaling pathways in the liver and intestinal tract.[22] Negative feedback inhibition by bile acids on farsenoid X receptor alpha (FXRα) prevents activation of the bile acid synthesis pathway.[22] FXR is a nuclear receptor found in the liver and other organs including the intestine. Bile acid-activated FXR promotes expression of small heterodimer partner, promotes the enterohepatic bile acid circulation, and inhibits the transcription of apolipoprotein A-I.[23–25] Bile acid synthesis is regulated by small heterodimer partner, fibroblast growth factor 15/19 and another FXR–dependent pathway involving peroxisome proliferator-activated receptor.[21] Bile acids also alter expression of numerous genes involved in the regulation of glucose, fatty acids, lipoprotein synthesis, and metabolism and play an important role in triglyceride regulation.[22]

Colesevelam is an anion-binding resin that binds the negatively charged bile acids in the intestine, forming an insoluble complex which is excreted in feces.[26] Colesevelam has high affinity for both trihydroxy- and dihydroxy bile acids leading to increased fecal bile acid excretion compared to older BAS.[27] This depletes the bile acid pool, leading to altered hepatic cholesterol homeostasis and interruption of the enterohepatic circulation of bile acids. Reduction in intracellular cholesterol leads to increased transcription and stimulation of HMG-CoA reductase to increase hepatic cholesterol production which is shunted into bile acid synthesis.[28] Hepatic LDL receptor expression increases with the decrease in circulating serum cholesterol levels (increased catabolism of cholesterol to bile acids) and reduction in serum LDL-c levels due to increased clearance of LDL-c from the blood.[19] Depletion of bile acids in the enterohepatic circulation leads to a decrease in the usual interaction between bile acids and FXR.[29] Consequently, reduced FXR activation leads to decreased expression of small heterodimer partner, which normally inhibits Liver X receptor (LXR).[23] Loss of negative feedback inhibition on LXR leads to increased hepatic production of triglycerides and increased serum HDL-c via increased apolipoprotein A-I (apo A-I) expression.[30]

FXRα regulates glucagon synthesis and gluconeogenesis. Through the activation of FXRα, bile acids act as signaling molecules in glucose homeostasis pathways and increased LXR activity leads to blood glucose reduction.[31,32] Bile acids also promote the secretion of glucagon-like peptide 1 via activation of the G-protein coupled receptor TGR5.[33] Through effects on hepatocyte nuclear factor 4, bile acids might also affect the expression of hepatic gluconeogenesis genes.[34]

Metabolism

Colesevelam is not absorbed from the intestinal tract, and has no significant volume of distribution, plasma protein binding or renal clearance.[18]

Pharmacokinetic profile

One study demonstrated an almost a three-fold increase in fecal excretion of bile acids in subjects administered colesevelam 2.3- or 3.8 g/d for 4 weeks.[35] Most of the LDL-c reducing effect is seen in the first 2-weeks of therapy.[36] Cross-linking of polyallylamine with epichlorohydrin decreases the probability of negative interactions between colesevelam and the gut lining.[37] Its water-retaining property allows for the creation of a soft, gelatinous-like material and this has also been postulated as an explanation for the reduced gastro-intestinal irritation compared to other bile acid sequestrants.[27] Both once daily or twice daily (split dosing) have been shown to be effective for lipid-lowering effects.[19] The bile acid salt binding of colesevelam is not affected by suspension of colesevelam with common beverages.[18,38]

Drug-drug interaction

The polymer structure of colesevelam and the cross-linking epichlorohydrin structure reduce systemic absorption, potential drug interactions and interactions with the gastrointestinal tract.[26] Several drug-drug interactions were noted in the manufacturer's prescribing information.[18] Simultaneous administration of colesevelam has been shown to decrease the intestinal absorption, area under the curve (AUC), and C_{max} of levothyroxine, the hormones ethinyl-estradiol and norethindrone in oral contraceptives, and glyburide. A 4-hour interval between ingestion of colesevelam and these drugs is recommended. No interactions were noted for metformin. The C_{max} of repaglinide was reduced with simultaneous administration of colesevelam, but no effect observed on its AUC.

Colesevelam does not affect the absorption of vitamins A, D and K unlike standard BAS.[18] However, caution is recommended when administering colesevelam to patients with susceptibility to fat-soluble vitamin deficiencies or vitamin K deficiencies. Colesevelam has no significant interactions with digoxin, warfarin, metoprolol, quinidine and valproic acid.[39] Verapamil sustained release absorption and bioavailability were noted to be decreased in some patients, but this significance remains unclear given inter-individual variability.

Simultaneous administration of colesevelam with statins does not reduce their bioavailability, but has rather been shown to have additive LDL-c reduction effect.[40–42] No significant interaction has been shown during colesevelam and fenofibrate co-administration or after a 4-hour dosing interval.[43] Although studies have not evaluated any interaction between colesevelam and ezetimibe, significant further reduction in LDL-c levels occurs with combined colesevelam-ezetimibe therapy.[44–46]

Contraindications

Colesevelam is contra-indicated in patients with history of hypersensitivity to any of its constituents, in patients with serum triglyceride levels >500 mg/dl, history of pancreatitis secondary to hypertriglyceridemia, dysbetalipoproteinemia, history of bowel obstruction or at high risk for bowel obstruction.[18]

Efficacy

Monotherapy

Randomized trials of colesevelam monotherapy are summarized in Tables 1 and 2. These trials were performed in hypercholesterolemic populations with mean LDL-c levels of 146–194 mg/dl and triglyceride levels of 114 to 203 mg/dl. At the recommended dose of 3.75 mg/d, colesevelam reduced LDL-c by 9% to 20% and increased triglycerides from 6 to 25%. Colesevelam also decreased C-reactive protein by 19% and LDL-particle number by 14% in the single trials in which they were measured.[49]

Davidson et al, in a multicenter, randomized clinical trial, demonstrated a dose-dependent LDL-c reduction from baseline in the colesevelam groups (–2% to –19%).[27] LDL-c reduction was significant for the colesevelam 3.0 g/day and 3.75 g/day groups (–9%, and –19%, respectively). A significant 8% decrease from baseline total cholesterol (TC) level occurred with colesevelam 3.75 g/day group. Significant increases (+8%, p = 0.02 and +11%) in HDL-c level were noted in the 3.75 and 3.0 g/d colesevelam groups respectively. Baseline triglycerides were 155–175 mg/dl. An modest upward trend in triglycerides did not achieve statistical significance. Rosenson et al, further analyzed the effect of colesevelam on LDL particle size.[47] A significant reduction in mean LDL particle number (–7% and –14%) occured in the colesevelam 3.0- and 3.75 g/day groups, respectively. Mean LDL-particle size increased by 1% only in the colesevelam 3.75 g/day group.

Insull et al, in a randomized, clinical trial showed significant reduction from baseline in all colesevelam groups for both mean serum LDL-c (–9% to –15%) and mean serum TC (–4% to –10%).[36] All colesevelam groups showed a significant increase of 3 to 4% in median HDL-c from baseline. Median serum triglyceride increased by 5% to 10% in both placebo and colesevelam groups. ApoB levels were reduced (6%–12%) in dose dependent response in all colesevelam groups, while Apo A-I increased in the colesevelam 2.3 g/day and 3.0 g/day groups.

Deveraj et al, found a significant reduction in both LDL-c levels (–9%) and hs-CRP levels (–16%) in the colesevelam group.[48] No significant changes were noted in total triglyceride or HDL-c levels in either placebo or colesevelam groups.

Donovan et al,[64] showed reduction in both mean LDL-c (–10% to –13%) and TC (–5% to –6%) in colesevelam 2.3 g/day and 3.8 g/day groups in their open-label study. A significant 24% increase in mean triglcyeride level ($p < 0.05$) occurred in the 3.8 g/day group.

Combination therapy

Randomized trials of colesevelam used in combination with statins, ezetimibe, and fenofibrates are summarized in Tables 1 and 2. Baseline LDL-c in these trials ranged from 130 to 202 mg/dl and triglycerides ranged from 115 to 230 mg/dl. When compared to low or moderate dose statin therapy, the addition of colesevelam decreased LDL-c an additional 6% to 16%. Coadministration with a statin markedly attenuated the hypertriglyceridemia observed with colesevelam monotherapy. Modest increases in HDL-c were also observed with the addition of colesevelam to statin

Table 1. Baseline characteristics of trials of colesevelam used as monotherapy and in combination with other lipid-lowering medications or anti-diabetes medications.

Study	Agent (Drug)/day	Study baseline characteristics									
		n	Mean age	% Men	% Women	% Diabetes	% CHD	LDL-c	Total-C	HDL-c	Trig
Monotherapy											
Davidson et al[27]	Placebo	29	57.1	45	55	NA	NA	194	281	53	169
	Colesevelam 1.5 g	30	NA	NA	NA	NA	NA	186	NA	NA	175
	Colesevelam 2.25 g	29	NA	NA	NA	NA	NA	187	NA	NA	160
	Colesevelam 3.0 g	30	56	NA	NA	NA	NA	182	NA	NA	155
	Colesevelam 3.75 g	29	56	NA	NA	NA	NA	178	NA	NA	175
Insull et al[36]	Placebo	NA	56	NA	NA	NA	NA	NA	NA	NA	NA
	Colesevelam 2.3 g	NA	56	NA	NA	NA	NA	NA	NA	NA	NA
	Colesevelam 3.0 g	NA	56	NA	NA	NA	NA	NA	NA	NA	NA
	Colesevelam 3.8 g	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
	Colesevelam 4.5 g	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Deveraj et al[48]	Placebo	23	NA	NA	NA	NA	NA	158	236	54	114
	Colesevelam 3.75 g	25	NA	NA	NA	NA	NA	150	234	53	127
Donovan et al[40]	Colesevelam 2.3 g	12	56	NA	NA	NA	NA	146	232	48	192
	Colesevelam 3.8 g	12	56	NA	NA	NA	NA	158	248	51	203
Combination therapy											
Davidson et al[49]	Placebo	26	57	50	50	NA	NA	171	256	51	167
	Colesevelam 2.3 g	29	54	55	45	NA	NA	172	254	49	173
	Lovastatin 10 mg	26	56	42	58	NA	NA	168	253	50	175
	Colesevelam + Lovastatin (dosed together)	27	63	33	67	NA	NA	174	260	51	180
	Colesevelam + Lovastatin (dosed apart)	23	59	44	56	NA	NA	169	256	56	154
Knapp et al[41]	Placebo	33	55	52	48	NA	NA	184	268	48	183
	Colesevelam 2.3 g	36	58	42	58	NA	NA	186	270	50	163
	Colesevelam 3.8 g	37	53	54	46	NA	NA	198	282	49	172
	Simvastatin 10 mg	35	56	46	54	NA	NA	183	265	50	152
	Simvastatin 20 mg	39	54	62	38	NA	NA	180	262	48	153
	Colesevelam 2.3 g + Simvastatin 20 mg	37	53	54	46	NA	NA	191	274	47	172

(*Continued*)

Table 1. (*Continued*)

Study	Agent (Drug)/day	Study baseline characteristics									
		n	Mean age	% Men	% Women	% Diabetes	% CHD	LDL-c	Total-C	HDL-c	Trig
	Colesevelam 3.8 g + Simvastatin 10 mg	34	54	62	38	–	NA	196	274	49	132
Hunninghake et al[42]	Placebo	19	57	79	21	NA	NA	185	263	46	151
	Colesevelam 3.8 g	17	57	41	59	NA	NA	184	271	47	166
	Atorvastatin 10 mg	19	58	47	53	NA	NA	182	268	49	176
	Atorvastatin 80 mg	20	61	55	45	NA	NA	182	265	47	153
Bays et al[50]	Colesevelam 3.8 g + Atorvastatin 10 mg	19	53	79	21	NA	NA	187	270	46	153
	Statin + Placebo	69	58	46	54	14	6	130	212	52	154
	Statin + Colesevelam (various doses)	134	57	44	56	13	10	133	214	52	137
Bays et al[44]	Placebo + ezetimibe 10 mg	43	57	35	65	5	7	175	260	58	115
	Colesevelam 3.8 g + ezetimibe 10 mg	43	61	51	49	12	7	177	264	58	137
Knopp et al[51]	Placebo + ezetimibe 10 mg	10	57	40	60	0	NA	167	NA	NA	134
	Colesevelam 3.8 g + ezetimibe 10 mg	10	57	60	40	0	NA	158	NA	NA	140
Zema et al[45]	Ezetimibe 10 mg	6	64	NA	NA	NA	NA	202	279	45	158
	Colesevelam 3.8 g	6	64	NA	NA	NA	NA	177	258	58	132
	Colesevelam added to ezetimibe	6	64	NA	NA	NA	NA	150	229	48	164
	Ezetimibe added to colesevelam	6	64	NA	NA	NA	NA	137	227	58	163
McKenney et al[52]	Fenofibrate 160 mg + Placebo	65	55	57	43	12	NA	157	253	46	217
	Fenofibrate + Colesevelam 3.8 g	64	55	55	45	9	NA	160	256	45	230
Moore et al[53]	Atorvastatin 10–80 mg	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
	Atorvastatin 10–80 mg + Niacin ER 2 g + Placebo	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
	Atorvastatin 10–80 mg + Niacin ER 2 g + Colesevelam 3.75 g	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Combination with diabetes therapy											
Fonseca et al[54]	Placebo + sulfonylurea ± other oral antidiabetes drug	231	57	53	47	100	NA	NA	NA	NA	NA
	Colesevelam 3.75 g + sulfonlyurea ± oral antidiabetes drug	230	57	56	44	100	NA	NA	NA	NA	NA

Bays et al[55]	Placebo + metformin ± other oral antidiabetes drug	157	57	55	47	100	NA	99	181	45	166
	Colesevelam 3.75 g + metformin ± oral antidiabetes drug	159	56	51	49	100	NA	106	190	45	172
GLOWS[56]	Placebo + oral anti-diabetes drug	34	56	59	41	100	NA	120	196	44	214
	Colesevelam 3.75 g + oral antidiabetes drug	31	57	52	48	100	NA	123	208	48	182
Goldberg et al[57]	Placebo + insulin ± other oral antidiabetes drug	140	56	51	49	100	NA	102	183	44	167
	Colesevelam 3.75 g + insulin ± oral antidiabetes drug	147	57	52	48	100	NA	102	178	42	155

Abbreviations: CHD, coronary heart disease; HDL-c, high density lipoprotein cholesterol; LDL-c, low-density lipoprotein cholesterol; NA, not available; Total-C, total cholesterol; Trig, triglycerides.

therapy. Colesevelam resulted in improvements in LDL-c (−11%) and non-HDL-c (−7%) when added to fenofibrate without worsening triglyceride levels. Coadministration of colesevelam with ezetimibe provided variable additional LDL-c reductions ranging from 0 to 20% over ezetimibe alone, and triglyceride responses were similarly variable. Colesevelam also provided a non significant additional 10% reduction in LDL-c when added to statin-niacin therapy, and did not increase triglycerides.

Combination with statins

Davidson et al, performed a randomized study comparing colesevelam monotherapy, lovastatin monotherapy, and combination therapy with colesevelam 2.3 g/day + lovastatin 10 mg/day administered either simultaneously or 4 hours apart.[49] Mean serum LDL-c levels were reduced by 32% to 34% in both combination therapy groups compared to monotherapy with colesevelam or lovastatin (−7% versus −22%, respectively). A significant increase in serum HDL-c levels occurred only in the colesevelam monotherapy group (5%). Apo A-I increased significantly in each active treatment group except for the 4-hour apart combination group. With ApoB, there was reduction with each treatment group, however, the reduction was greater in the combination groups (−24%), compared to lovastatin monotherapy (−16%). Only colesevelam monotherapy had a significant effect (+14%) on triglycerides level.

Knapp et al, compared the lipid-lowering effects of colesevelam 2.3 or 3.8 g monotherapy, simvastatin 10 or 20 mg, colesevelam 3.8 g + simvastatin 10 mg or colesevelam 2.3 g + simvastatin 20 mg/day for 6 weeks.[41] Both combinations of colesevelam with simvastatin reduced mean serum LDL-c by 42% from baseline. Colesevelam 3.8 g + simvastatin 10 mg reduced LDL-c by an additional 16% compared to simvastatin 10 mg monotherapy. Median HDL-c increased modestly in all active treatment groups except in the colesevelam 3.8 g/day monotherapy group. Triglyceride reductions of 12% to 17% were observed in both the statin monotherapy and statin-colesevelam groups, compared to consistent 11% increases at both dosages of colesevelam. Mean apoB decreased from baseline by 4%–33% in all treatment groups, with the greater percent reduction in the combination therapy groups. Apo A-I increased significantly from baseline in all

Table 2. Results of trials of colesevelam used as monotherapy and in combination with other lipid-lowering medications or anti-diabetes medications.

Study	Agent (Drug) g/day	Percent change from baseline									
		LDL-c	HDL-c	Median TG	TC	Non-HDL-c	Apo B	Apo A-I	LDL-p N	LDL-p size	hs-CRP
Monotherapy											
Davidson et al[27]	Placebo	–0.1	–0.8	+3.7	–0.1	NA	NA	NA	NA	NA	NA
	Colesevelam 1.5	–1.8	+2.2	+2.2	–1.6	NA	NA	NA	NA	NA	NA
	Colesevelam 2.25	–4.9	+2.2	–1.6	–4.1	NA	NA	NA	NA	NA	NA
	Colesevelam 3.0	–9.1*	+11.2*	+1.8	–4.8	NA	NA	NA	NA	NA	NA
	Colesevelam 3.75	–19.1**	+8	+6.4	–8.1**	NA	NA	NA	NA	NA	NA
Rosenson et al[47]	Placebo	+4.5*	NA	–0.2	NA	NA	NA	NA	+3.9	+0.2	NA
	Colesevelam 1.5	–3.6	NA	+3.3	NA	NA	NA	NA	–0.9	+0.3	NA
	Colesevelam 2.25	–3.8	NA	+1.9	NA	NA	NA	NA	+1.1	+0.4	NA
	Colesevelam 3.0	–9.5**	NA	+4.8	NA	–6.8	NA	NA	–6.8*	+0.1	NA
	Colesevelam 3.75	–11.3 **	NA	+23.1*	NA	–13.7**	NA	NA	–13.7**	+1.1*	NA
Insull et al[36]	Placebo	0	–1	+5*	+1	NA	0	NA	NA	NA	NA
	Colesevelam 2.3	–9**	+3**	+9*	–4**	NA	–6*	NA	NA	NA	NA
	Colesevelam 3.0	–12**	+4**	+5*	–6**	NA	–8*	NA	NA	NA	NA
	Colesevelam 3.8	–15**	+3**	+ 10**	–7**	NA	–12*	NA	NA	NA	NA
	Colesevelam 4.5	–18**	+3**	+9*	–10**	NA	–12*	NA	NA	NA	NA
Deveraj et al[48]	Placebo	–5.6	–1.9	+10.5	–3.8	NA	NA	NA	NA	NA	NA
	Colesevelam 3.75	–9.3*	0	+25.1	–3.8	NA	NA	NA	NA	NA	–15.9*
Donovan et al[64]	Colesevelam 2.3	–10*	+6*	+1.5a	–5	NA	NA	NA	+3.9	+0.2	NA
	Colesevelam 3.8	–13	–2	+24.1*	–6	NA	NA	NA	NA	NA	NA
Combination therapy											
Davidson et al[49]	Placebo	+1	+1	+2	+1	NA	0	0	NA	NA	NA
	Colesevelam 2.3	–7*	+4	+14**	–3	NA	–3	+8**	NA	NA	NA
	Lovastatin 10	–22**	+3	+5	–15**	NA	–16**	+5*	NA	NA	NA
	Colesevelam + Lovastatin (dosed together)	–34**	+3	+9	–21**	NA	–24**	+5*	NA	NA	NA
	Colesevelam + Lovastatin (dosed apart)	–32**	+3	–3	–21**	NA	–24**	+4	NA	NA	NA
Knapp et al[41]	Placebo	–4	–3	+6	–2	NA	–4*	0	NA	NA	NA
	Colesevelam 2.3	–8**	+3	+11	–4*	NA	–6*	+6*	NA	NA	NA

	Colesevelam 3.8	–16**	+2	+11	–9**	NA	–14**	+4*	NA	NA	NA
	Simvastatin 10	–26**	+3	–17*	–19**	NA	–20**	+5*	NA	NA	NA
	Simvastatin 20	–37	+7a	–12*	–23**	NA	–26**	+7*	NA	NA	NA
	Colesevelam 2.3 + Simvastatin 20	–42**	+4a	–12*	–29**	NA	–32**	+10**	NA	NA	NA
	Colesevelam 3.8 + Simvastatin 10	–42**	+10a**	–12	–28**	NA	–33**	+10**	NA	NA	NA
Hunninghake et al[42]	Placebo	+3	+4*	+9	+4	NA	+2	+5	NA	NA	NA
	Colesevelam 3.8	–12*	+3*	+ 10	–6*	NA	–10*	+4*	NA	NA	NA
	Atorvastatin 10	–38**	+8*	–24*	–27**	NA	–32	+2	NA	NA	NA
	Atorvastatin 80	–53***	+5*	–33**	–39***	NA	–46*	–3	NA	NA	NA
	Colesevelam 3.8 + Atorvastatin 10	–48***	+11*	–1	–31***	NA	–38*	+9*	NA	NA	NA
Bays et al[50]	Statin + Placebo	–6.5	–0.4	–4.1	–3.4	NA	–5.8	–0.2	NA	NA	+17.2
	Statin + Colesevelam (various doses)	–15.7*	0	+16.3	–7.2*	NA	–8.3	+4.8*	NA	NA	–6.2*
Bays et al[44]	Placebo + ezetimibe 10	–21.4	+3.3	–2.8	–14.4	–19.5	–14.8	+1.3	NA	NA	+2.7
	Colesevelam 3.8 + ezetimibe 10	–32.3*	+3.4	+4.9	–20.3*	–26.7*	–22.7**	+6.7*	NA	NA	–15.4
Knopp et al[51]	Placebo + ezetimibe 10	–24	+0.9	–19	–19	–25	–31	NA	NA	NA	NA
	Colesevelam 3.8 + ezetimibe 10	–30	+5.0	+36*	–15	–21	–22	NA	NA	NA	NA
Zema et al[45]	Ezetimibe 10	–25.5*	+7.5	+4	–17.6*	–22.5"	NA	NA	NA	NA	NA
	Colesevelam 3.8	–20.3*	–1.1	+23.1	–11.9*	–15.6*	NA	NA	NA	NA	NA
	Colesevelam added to ezetimibe	–21.1*↕	–1.4↕	–0.4↕	–13.2↕	–16.4*↕	NA	NA	NA	NA	NA
	Ezetimibe added to colesevelam	–19.1**↕	–0.5↕	–3.0↕	–12↕	–16*↕	NA	NA	NA	NA	NA
McKenney et al[52]	Fenofibrate 160 + Placebo	–6	+10.3	–36.9	–9.9	–14.0	–14.0	+5.8	NA	NA	NA
	Fenofibrate + Colesevelam 3.8	–17**	+11.5	–32.2	–15.0**	–21.0**	–20.4**	+7.1	NA	NA	NA
Moore et al[53]	Atorvastatin 10–80 mg	–47	+12	–25	NA	NA	NA	NA	NA	NA	NA
	Atorvastatin 10–80 + Niacin ER 2 g + Placebo	–47	+25	–33	NA	NA	NA	NA	NA	NA	NA
	Atorvastatin + Niacin ER 2g + colesevelam 3.75	–57	+29	–42	NA	NA	NA	NA	NA	NA	NA
Combination with Diabetes therapy											
Fonseca et al[54]	Placebo + sulfonylurea ± other oral antidiabetes drug	+0.6	+0.3	+1.0	+0.1	+0.6	+0.8	+2.1	NA	NA	NA

(Continued)

Table 2. (*Continued*)

Study	Agent (Drug) g/day	Percent change from baseline								
		LDL-c	HDL-c	Median TG	TC	Non-HDL-c	Apo B	Apo A-I	LDL-p N	LDL-p size	hs-CRP
	Colesevelam 3.75 + sulfonlyurea ± oral antidiabetes drug	–16.1	+0.5**	+19.5**	–4.9**	–6.1**	–5.9**	+5.9**	NA	NA	0.4
Bays et al[55]	Placebo + metformin ± other oral antidiabetes drug	+2.2	–0.3	+10.5	+4.1	+3.6	+3.4	+2.8	NA	NA	NA
	Colesevelam 3.75 + metformin ± oral antidiabetes drug	–13.4*	+0.1	+19.5	–8.1**	–6.0**	–5.4**	+5.6	NA	NA	14.4%
GLOWS[56]	Placebo + oral anti diabetes drug	+2.1	–1.8	+23.1	+3.4	NA	+5.5	–0.3	NA	NA	NA
	Colesevelam 3.75 + oral antidiabetes drug	–9.6*	–3.3	+30.9	–4.0*	NA	–6.3*	+1.9	NA	NA	NA
Goldberg et al[57]	Placebo + insulin ± other oral antidiabetes drug	+0.5	+0.4	+0.3	+0.5	+0.8	+0.9	+2.5	NA	NA	+8.7
	Colesevelam 3.75 = insulin ± oral antidiabetes drug	–12.3**	–0.5	+22.7**	–12.3**	–3.2	–4.4*	+4.7	NA	NA	–3.0

Abbreviations: Apo, Apolipoprotein; HDL-c, High density lipoprotein cholesterol; LDL-c, Low-density lipoprotein cholesterol; LDL-p, Low-density lipoprotein particle; NA, Not available; Total-C, Total cholesterol; Trig, Triglycerides.

active treatment groups by 4%–10% with the greater increase in the combination therapy groups.

Hunninghake et al, performed a randomized clinical trial comparing colesevelam monotherapy, atorvastatin monotherapy and the combination therapy of colesevelam 3.8 g/day + atorvastatin 10 mg/day.[42] LDL-c was reduced by 48% with combination atorvastatin + colesevelam compared to –38% and 53% for atorvastatin 10 and 80 mg, respectively. Colesevelam alone and in combination combination therapy had neutral effects on serum triglycerides. HDL-c increased significantly in all treatment groups including placebo, with the greatest increase (+11%) with combination therapy. ApoB decreased significantly in all active treatment groups, with superior reductions (–46% and –38%) from high-dose atorvastation and combination therapy, respectively. No significant effects on Apo A-I level was obtained from atorvastatin monotherapy, unlike colesevelam mono-and combination therapy which significantly increased Apo A-I (4% and 9%).

Bays et al, performed a meta-analysis of three clinical trials in which colesevelam was added to either stable simvastatin, atorvastatin or pravastatin therapy and compared to placebo + statin.[50] Colesevelam + statin lowered mean LDL-c by an additional 9% and hs-CRP by an additional 23% compared to statin monotherapy. No differences were observed in median triglycerides, HDL-c, apo A-1, or apo B.

Combination with ezetimibe

A trial by Bays et al, randomized participants to colesevelam 3.8 g/day + ezetimibe 10 mg/day or to placebo + ezetimibe 10 mg/day.[44] Compared to ezetimibe + placebo, colesevelam + ezetimibe resulted in additional reductions in mean serum LDL-c (11%), non-HDL-c (7%), and apoB (8%). Median triglycerides were similar in both groups, although apo A-I was 5% higher in the colesevelam + ezetimibe group.

Knopp et al, performed a 12 week study in which patients were randomized to colesevelam 3.8 g + ezetimibe 10 mg or placebo + ezetimibe 10 mg/day.[51] LDL-c, non-HDL-c, and apo B reductions were similar in the 2 groups. However, triglyceride levels increased by 36% in the colesevelam + ezetimibe group compared to a –19% reduction in the placebo + ezetimibe group.

Zema, et al performed an open-label study, in which patients were initially on monotherapy with

either colesevelam 3.75 g/day or ezetimibe 10 mg daily for 6 weeks.[45] A second drug was added to their regimen for another 6 weeks. Ezetimibe added on to colesevelam therapy produced a further reduction of 19% in LDL-c and 16% in non-HDL-c. Similar reductions were observed when colesevelam was added to ezetimibe (21% and 16%, respectively). No significant additional changes occurred in HDL-c and triglyceride levels.

Combination with fenofibrate

McKenney et al, evaluated the efficacy of colesevelam combination therapy with fenofibrate in dyslipidemic individuals with mean LDL-c of 158 mg/dl and median triglycerides of 224 mg/dl.[52] Colesevelam 3.75 g/day or placebo was added to fenofibrate 160 mg/day for six weeks after an eight-week run-in monotherapy with fenofibrate. Colesevelam + fenofibrate led to an additional 11% LDL-c reduction compared to fenofibrate plus placebo. Combination therapy also lowered non-HDL-by an additional 7% and apo B by an additional 6%. No significant difference in triglyceride, HDL-c, or apo A-I levels were observed.

Combination with niacin and statin

Moore et al, performed a one year randomized study in which subjects were randomized to atorvastatin 10–80 mg monotherapy, combined therapy of atorvastatin 10–80 mg + extended release niacin 2 g, or triple therapy with atorvastatin 10–80 mg + extended release niacin 2 g + colesevelam 3.75 mg.[53] Triple therapy reduced LDL-c by 57% compared to 47% with atorvastatin monotherapy (all doses). However, the addition of niacin to atorvastatin, or the further addition of colesevelam did not significantly reduce LDL-c. HDL-c was increased by 29% with triple therapy, 25% with atorvastatin + niacin, and 12% with atorvastatin monotherapy. Triglycerides were reduced by 42% in triple therapy group, 33% in the atorvastatin + niacin groups, and 25% in the atorvastatin monotherapy group.

Diabetes

The lipid and glucose-lowering effects of colesevelam have been evaluated in combination with oral antiglycemic agents or insulin. Colesevelam reliably reduced hemoglobin A1c by 0.5% in individuals with inadequately controlled diabetes, and had lipid effects similar to non-diabetic populations. However, there was a tendency to greater triglyceride increases with colsevalam.

Fonseca et al, randomized subjects with Type II diabetes inadequately controlled on sulfonylurea-based therapy to either placebo or colesevelam 3.75 g/d for 26 weeks.[54] Baseline hemoglobin A1c levels of 8.3% were decreased by 0.5% compared to placebo, with no change in background diabetes medications. Rates of background statin therapy and baseline lipids were not reported. The colesevelam group experienced a 17% greater reduction in LDL-c along with 7% greater reductions in non-HDL-c and apoB. Median triglyceride levels at baseline were not reported but an 18% increase in triglycerides occurred with colesevelam compared to placebo.

Bays et al, randomized subjects with Type II diabetes inadequately controlled on metformin-based therapy to colesevelam 3.75 g/d to or placebo.[55] Baseline hemoglobin A1c levels were 8.1% and colesevelam lowered mean HgbA1c by 0.5% compared to placebo. Approximately 45% of subjects were taking a statin at baseline and mean LDL-c levels were approximately 103 mg/dl. The colesevelam group experienced a 16% greater reduction in LDL-c (from 106 to 92 mg/dl), along with a 10% greater reductions in non-HDL-c (from 145 to 136 mg/dl) and an 8% greater reduction in apoB (117 to 110 mg/dl). Colesevelam also lowered hs-CRP by 14% (from 3.0 to 2.9 mg/L). Baseline triglyceride levels were approximately 170 mg/dl, and no significant increases were noted in triglycerides, or in HDL-c or apo A-I.

In the Glucose Lowering Effect of WelChol Study (GLOWS) performed by Zieve et al, subjects with Type II diabetes inadequately controlled on oral hypoglycemic agents were randomized to either placebo or colesevelam for 12 weeks.[56] Hemoglobin A1c was reduced by 0.5% with colesevelam, with a 1% reduction when hemoglobin A1c levels were ≥8.0%. Colesevelam had superior reductions in mean LDL-c from 123 to 108 mg/dl (12%), as well as in apoB (12%), and LDL-particle concentration (131 nmol/l). Colesevelam increased the median triglycerides of 183 mg/dl to 230 mg/dl, although this was not significantly different from placebo.

Goldberg et al, evaluated patients with Type II diabetes inadequately controlled on insulin–based hypoglycemic regimens who were randomized to

either colesevelam 3.75 g/day or placebo.[57] Glycated hemoglobin reduced by –0.5% compared to placebo. Almost 60% were on a statin with mean baseline LDL-c 102 mg/dl and non-HDL 137 mg/dl. Colesevalam reduced LDL-c by 13%, non-HDL-c by 4% and apo B by 5%. Baseline triglycerides were 161 mg dl and increased 22% compared to placebo. hs-CRP was reduced by 19% in the colesevelam group.

Safety

Colsevelam is a non-absorbed polymer which reduces the potential for adverse events. Table 3 summarized the adverse effects and drug discontinuation rates in colesevelam trial. In a 6-week study, Davidson et al, found that both low and high doses of colesevelam were well-tolerated with no statistically significant difference in adverse events experienced in placebo versus colesevelam.[27] The most treatment related common side effects were gastrointestinal (flatulence and constipation). At the study conclusion, no clinically significant changes from baseline occurred in serum chemistry labs, kidney function, hematological labs, vitamin A and E, prothrombin time, partial thromboplastin time, estradiol levels, body weight, pulse and blood pressure. A non-dose related increase in alkaline phosphatase did occur. In the 3.75 g colesevelam group, alanine aminotransferase and aspartate aminotransaminase levels increased, but remained within normal parameters. The most common adverse events in a 24-week trial were flatulence (11%), constipation (10%), dyspepsia (6%) and diarrhea, although there was no significant difference in frequency between placebo and colesevelam.[36] Other clinical trials have not demonstrated any significant clinical changes in laboratory parameters.[55]

Meta-analysis of three colesevelam + statin clinical trials, showed that no serious drug-related adverse events occurred.[50] The incidence of drug-related adverse events for colesevelam plus pravastatin, atorvastatin or simvastatin were 13%, 20% and 26% respectively, compared to statin + placebo (0%–13%). Less than 5% of patients in either group dropped out from the trials due to adverse events.

Studies to evaluate cancer risk in humans are lacking. Rats given 20–40 times the maximum human dose had an increased incidence of pancreatic acinar cell adenoma and C-cell adenoma.[58] Animal studies show that colesevelam does not affect fertility or cause maternal or fetal toxicity in rats and rabbits.[59, 60] Colesevelam is a pregnancy B medication.[18]

Patient Preference

Davidson et al, found that overall compliance with different doses of colesevelam was more than 93%.[27] Other trials show compliance of >90% with colesevelam 3.75 mg monotherapy or in combination with other drugs.[36,44,51,54,55,57] In the meta-analysis by Bays et al, of 3 randomized, placebo-controlled trials of combination colesevelam with statins, less than 5% of subjects with-drew from the studies due to medication-related adverse events.[50]

Place in Therapy

A meta-analysis of diet, monotherapy with bile acid sequestrants and statins, and ileal bypass surgery found that coronary heart disease risk was reduced in direct proportion to the degree of LDL-c lowering.[61] Although no cardiovascular endpoint trials have been performed with colesevelam, several trials of cholestyramine and colestipol have demonstrated improvement in atherosclerotic progression and reductions in cardiovascular events. The largest trial of bile acid sequestrant monotherapy, the Lipid Research Clinics Coronary Primary Prevention Trial, found that 7.4 years of cholestyramine lowered LDL-c by 13% and reduced nonfatal myocardial infarction and coronary heart disease death by 19% in men with hypercholesterolemia who were free of cardiovascular disease at baseline.[62] A trial in men with coronary heart disease found that colestipol to lower LDL-c by 13% also reduced recurrent coronary events.[63] Several trials evaluating colestipol or cholestyramine in combination with niacin and statins found a decrease in angiographic progression of coronary artery disease compared to placebo or usual care.[64–66] Few data are available from trials comparing statins used in combination to statin monotherapy.

Current guidelines recommend therapeutic lifestyle changes for all patients requiring LDL-c reduction.[3] Taken together, weight loss, regular physical activity, dietary modifications, stanol/sterol products, and soy protein can lower LDL-c by 15%–20%. The recommendation to consume 25–30 grams per day of total dietary fiber includes 7–13 grams of soluble fiber, which will lower LDL-c 3% to 5%.

Table 3. Adverse events in trials of colesevelam used as monotherapy and in combination with other lipid-lowering medications or anti-diabetes medications.

Study	Treatment related adverse events (TRAE)	With-drew due to drug-related adverse event (DRAE)	Laboratory parameters and vital signs	Severity of drug-related adverse events (DRAE)
Davidson et al[27] Colesevelam (n = 118) Placebo (n = 29)	**Colesevelam group:** Flatulence (30%), Constipation (20%), Dyspepsia (16%), Diarrhea (10%), Nausea (6%) **Placebo group:** Flatulence (7%), Constipation or diarrhea (0%), Dyspepsia (3%), Nausea (0%)	**In colesevelam group:** 4 subjects **In placebo group:** 0 subjects	No clinically significant changes in serum chemistry, hematologic parameters, serum vitamin A or E. Prothrombin time, partial thromboplastin time, estradiol levels, body weight and vital signs Increase in alkaline phosphatase (ALP) in the colesevelam 1.5 g/day ($p = 0.01$) and 3.0 g/day ($p < 0.001$) groups Increase in alanine aminotransferase (ALT): $p < 0.001$ and aspartate aminotransferase (AST): $p = 0.02$ in the colesevelam 3.75 g/day group	**Colesevelam group:** NA **Placebo group:** NA
Rosenson et al[47]	See Davidson et al[27]	See Davidson et al[27]	See Davidson et al[27]	See Davidson et al[27]
Insull et al[36]	**Colesevelam group:** NA **Placebo group:** NA	**In Colesevelam group:** 31 subjects **In Placebo group:** 4 subjects	No clinically significant changes in serum chemistry, hematology, vitamin A, prothrombin or partial thromboplastin time	**Colesevelam group:** No serious DRAE **Placebo group:** No serious DRAE
Deveraj et al[48] Colesevelam (n = 25) Placebo (n = 23)	**Colesevelam group:** Nausea and bloating **Placebo group:** Nausea and bloating	**In colesevelam group:** 6 subjects (NA if due to DRAE) **In placebo group:** 6 subjects (NA if due to DRAE)	NA	**Colesevelam group:** NA **Placebo group:** NA
Donovan et al[40] Colesevelam (n = 24)	**Colesevelam 2.3 group:** Flatulence (25%), Nausea (17%), Diarrhea (8%) **Colesevelam 3.8 group:** Flatulence (8%), Nausea (17%), Diarrhea (8%)	1 subject in the 2.3 g/day group	No clinically significant changes in blood chemistry, hematology, vital signs or physical examination	No serious AE

(*Continued*)

Table 3. (*Continued*)

Study	Treatment related adverse events (TRAE)	With-drew due to drug-related adverse event (DRAE)	Laboratory parameters and vital signs	Severity of drug-related adverse events (DRAE)
Combination therapy				
Davidson et al[49] Placebo (n = 23) Colesevelam monotherapy (CM): n = 28 Colesevelam + Lovastatin (C + L) n = 48 Lovastatin monotherapy (LM) n = 25	**Diarrhea:** Placebo (8%) CM (3%), C + L (15%), LM (15%) **Constipation:** Placebo (4%) CM (10%), C + L (11%), LM (0%) **Myalgia:** Placebo (0%), CM (0%), C + L (7%), LM (12%)	**5 subjects:** (NA if these were DRAE) CM: (1 subject) C + L: (4 subjects)	No clinically significant changes in serum chemistry, hematology, liver function tests or vital signs	None
Knapp et al[41] Placebo (n = 33) Colesevelam monotherapy (CM): n = 73 Colesevelam + Simvastatin (C + S) n = 71 Simvastatin monotherapy (SM): n = 74	**Flatulence:** Placebo (17%) CM (26%), C + S (19%), SM (27%) **Constipation:** Placebo (14%), CM (31%), C + S (22%), SM (27%) **Diarrhea:** Placebo (9%), CM (3%), C + S (9%), SM (19%)	**13 subjects:** (NA if these were DRAE) Placebo (3 subjects) CM: (5 subjects) SM: (1 subject) C + S: (4 subjects)	No clinically significant changes in serum chemistry, hematology or vital signs	None
Hunninghake et al[42] Placebo (n = 19) Colesevelam monotherapy (CM): n = 17 Atorvastatin monotherapy (AM): n = 39 Colesevelam + Atorvastatin (C + A): n = 19	**Flatulence:** Placebo (10%), CM (0%), C + A (26%), AM (26%) **Constipation:** Placebo (5%) CM (6%), C + A (21%), AM (10%) **Diarrhea:** Placebo (16%) CM (0%), C + A (0%), AM (10%)	**5 subjects:** (NA if DRAE) CM: (1 subject) AM: (3 subjects) C + A: (1 subject)	No clinically significant changes in serum chemistry, hematology or vital signs Statistically significant increase for ALT (within normal range) in CM, AM (atorvastatin 80 mg/day) and C + A Statistically significant increase in ALP for CM, atorvastatin 80 mg/day and C + A Minor changes in direct bilirubin in AM and bicarbonate with placebo and AM	NA
Bays et al[50] Colesevelam + statin (n = 127 intent-to-treat population) Colesevelam + Simvastatin (C + S) Colesevelam + Atorvastatin (C + A) Colesevelam + Pravastatin (C + P) Placebo + statin (n = 67)	**In colesevelam + statin group:** **a) Constipation:** C + S (8.5%), C + A (12.5%), C + P (0%) **b) Dyspepsia:** C + S (8.5%), C + A (5%), C + P (0%) **c) Diarrhea:** C + P (2.1%)	Less than 5% of patients in either colesevelam + statin or placebo + statin groups	NA	No serious DRAE

	d) Nausea: C + P (4.3%) **In placebo + statin group:** Constipation 0%, Dyspepsia 4%			
Bays et al[44] Colesevelam + ezetimibe (C + E): n = 43, Placebo + ezetimibe (P + E): n = 43	**In C + E group:** Abdominal distention (7%) Constipation (7%), Dyspepsia (11.6%), Flatulence (7%) **In P + E group:** Abdominal distention and dyspepsia (0%), Constipation (4.7%), flatulence (2.3%)	**In C + E group:** 1 subject **In P + E group:** None	No clinically significant changes in serum chemistry, hematology or urinalysis	**In C + E group:** None **In P + E group:** None
Knopp et al[51] Colesevelam + ezetimibe (C + E): n = 10 Placebo + ezetimibe (P + E): n = 10	**In C + E group:** Stomach upset, nausea (1 subject) **In placebo group:** None	**In C + E group:** 1 subject **In P + E group:** 0 subject	No significant differences between treatment groups in AST levels	**In C + E group:** No serious DRAE reported **In P + E group:** No serious DRAE reported
Zema et al[45] 12 subjects participated	Not reported	None	No significant difference in ALT level or creatine kinase levels	None reported
McKenney et al[52] Fenofibrate + Colesevelam (F + C): n = 64 Fenofibrate + placebo (F + P): n = 65	**In F + C group:** Constipation (9.4%) Myalgia (0%) **In F + P group:** Constipation (7.7%) Myalgia (3.1%)	**In F + C group:** 2 subjects (3.1%) **In F + P group:** 4 subjects (6.2%)	1 subject (1.6%) in the F + C group had ALT and/or AST > 3 times the upper limit of normal No other clinically significant changes in labs, vital signs or physical findings	**In F + C group:** No serious DRAE **In F + P group:** No serious DRAE
Combination with diabetes therapy				
Moore et al[53]	NA	NA	NA	NA
Fonesca et al[54] Sulfonylurea + Colesevelam (S + C): n = 230 Sulfonylurea + Placebo (S + P): n = 231	**In S + C group:** Constipation (6.1%) Hypoglycemia (6 subjects) **In S + P group:** Constipation (2.6%) Hypoglycemia (2 subjects)	**In S + C group:** 12 subjects **In S + P group:** 4 subjects	Mean changes were similar in both groups. No weight gain	**In S + C group:** 3 severe DRAE No serious DRAE **In S + P group:** 1 severe DRAE No serious DRAE
Bays et al[55] Metformin-based + Colesevelam (M + C): n = 159 Metformin-based + Placebo (M + P): n = 157	**In M + C group:** Constipation (8.2%) **In M + P group:** Constipation (1.3%)	**In M + C group:** 6 subjects **In M + P group:** 2 subjects	No clinically relevant changes in lab parameters or vital signs. No weight gain	**In M + C group:** No severe DRAE No serious DRAE **In placebo group:** No severe DRAE No serious DRAE

(*Continued*)

Table 3. (*Continued*)

Study	Treatment Related Adverse events (TRAE)	With-drew due to drug-related adverse event (DRAE)	Laboratory parameters and vital signs	Severity of drug-related adverse events (DRAE)
GLOWS[56] Oral hypoglycemic agents + Colesevelam (n = 31) Oral hypoglycemic agents + Placebo (n = 34)	**In colesevelam group:** Gastrointestinal AE including constipation (22.6%) Constipation (19.4%) **In placebo group:** Gastrointestinal AE (8.8%) Constipation (0%)	**In colesevelam group:** 2 subjects **In placebo group:** 1 subject	No significant changes in weight	**In colesevelam group:** 61.3% were mild-moderate intensity 38.7% were severe intensity **In placebo group:** 50% were severe intensity No serious DRAE
Goldberg et al[57] Insulin regimen + Colesevelam (n = 147) Insulin-regimen + Placebo (n = 140)	**In colesevelam group:** Constipation (6.8%), Dyspepsia (3.4%), Hypoglycemia (3.4%), Flatulence (2.0%), Nausea (1.4%) **In placebo group:** Hypoglycemia (5.7%)	**In colesevelam group:** 5 subjects (3.4%) **In placebo group:** 2 subjects (1.4%)	Mean changes were similar in both groups. No significant weight gain	**In colesevelam group:** 13 (8.8%) severe DRAE No serious DRAE **In placebo group:** 11 (7.9%) severe DRAE No serious DRAE

In addition to lifestyle modifications, other options for lowering LDL-c in those who have not achieved their cholesterol goals with statin monotherapy include ezetimibe, niacin and fibrates.[3] Ezetimibe reliably reduces LDL-c by an additional 15% when coadministered with statin therapy, has few adverse effects, and excellent adherence.[11] However, questions remain regarding the additional cardiovascular benefits of adding ezetimibe to statin therapy. The ENHANCE (Ezetimibe and Simvastatin in Hypercholesterolemia Enhances Atherosclerosis Regression) trial found no difference in carotid intimal medial thickness progression between simvastatin 80 mg and simvastatin 80 mg and ezetimibe 10 mg, despite an additional 17% reduction in LDL-c with the addition of ezetimibe for 2 years.[67] The lack of benefit from added ezetimibe in ENAHNCE has been largely attributed to the low mean carotid intimal medial thickness at study entry, and on the high proportion of individuals receiving long-term LDL-c lowering therapy prior to study entry.[68] However, the recent SEAS (Simvastatin and Ezetimibe in Aortic Stenosis) found a less than expected 22% (95% CI 3%–37%) reduction ischemic cardiovascular events from the 50% LDL-c reduction from simvastatin 40 mg with ezetimibe 10 mg compared to placebo.[69] Based on the Cholesterol Treatment Trialists meta-analysis of 14 statin trials, the expected reduction in major cardiovascular event would have been 39%.[70] The most support for ezetimibe statin combination therapy comes from a *post hoc* analysis of the SANDS (Stop Atherosclerosis in Native Diabetic Study).[71] Those participants in the aggressively treated group who received ezetimibe-statin combination therapy had significantly more regression in carotid intimal medial thickness than those who received statin monotherapy, despite having higher on-treatment LDL-c levels (78 vs. 68 mg/dl, respectively).

Niacin 2 grams also lowers LDL-c when added to statin therapy, although the LDL-c lowering efficacy appears to be attenuated compared to niacin monotherapy.[12,13] Although gemfibrozil monotherapy has been shown to reduce cardiovascular events in dyslipidemic men with coronary heart disease, gemfibrozil typically increases LDL-c when added to statin therapy and combination gemfibrozil-statin therapy has significant safety concerns due to the increased risk of myopathy.[16,72,73] Fenofibrate and its active metabolite fenofibric acid more reliably lower LDL-c when used in combination with a statin, although the additional reductions are modest.[14,74] Although fenofibrate does not impair the glucuronidation of statins as does gemfibrozil, only modest reductions in cardiovascular risk have been observed in long-term trials.[72,75]

Other LDL-c lowering drugs have not been shown to influence glucose metabolism, and indeed niacin may worsen glucose tolerance in many patients.[76] Statins have also been found to modestly increased incident diabetes in some trials.[76,77] Therefore, colesevelam may have a unique role in patients with type 2 diabetes mellitus, for whom cardiovascular disease is the most common cause of morbidity and mortality, and in populations at high risk of developing diabetes.[3] Patients with type 2 diabetes mellitus often do not achieve either target cholesterol or glucose levels. One study found that 49% of patients with type 2 diabetes mellitus achieve the an LDL-c $<$ 100 mg/dl and 16% achieved LDL-c goal of $<$70 mg/dl.[78] Moreover, colesevalam lowers hemoglobin A1c by 0.5% to 1.0% in individuals with inadequately controlled diabetes on oral agents or insulin. This is a reduction in hemoglobin A1c similar to that observed for some of the newer incretin-based hypoglycemic agents, the dipeptidyl peptidase- (DPP-4) antagonists and glucagon-like peptide-1 (GLP-1) agonists.[79]

Although it is reassuring that colesevelam reduces C-reactive protein, reduces LDL particle number and increases LDL particle size when added to statin therapy, these parameters are not currently recommended as targets of therapy.[3,47,48,50]

Colesevelam may have application in special populations. In statin-intolerant patients, colesevelam can provide an alternative for cholesterol-lowering.[80] Since there has been heterogeneity of response in clinical trials of colesevelam combined with ezetimibe, additional LDL-c lowering efficacy should be demonstrated in the individual patient. For patients with transplanted organs, colesevelam is an alternative. Unlike statins, colesevelam does not affect the cytochrome P-450 system which is the enzyme system that cyclopsporine and tacrolimus (two common immunosuppressant agents) act upon to prevent transplant rejection. A cautious approach to dosing these drugs 4 hours before colesevelam is prudent.

Although colesevelam is contraindicated in patients with complete biliary obstruction, it may provide relief from pruritis due to cholestatic liver disease.[81,82] Colesevelam has been suggested for use as a phosphate binder in patients with end-stage renal disease and uremia, due to its structural similarity with colestimide.[83] Colesevelam has also been shown to be effective in treating irritable bowel syndrome-diarrhea predominant.[84]

The primary disadvantage of colesevelam is the increase in serum triglyceride levels secondary to its effect on reducing the hepatic bile acid pool and limiting bile acid inhibition of hepatic triglyceride synthesis. Use of colesevelam should be used cautiously when triglycerides are 200–400 mg/dl, and avoided entirely in patients with hypertriglyceridemia (>400 mg/dl).[81] Although complaints of constipation are much lower with colesevelam than the older bile acid sequestrants, colesevelam should be avoided in patients with reduced intestinal motility, recent abdominal surgery, or history of recent/repeated intestinal obstruction.

Although statins are a category X (risk of fetal abnormalities outweigh any possible benefit with therapy) and contraindicated in women who are pregnant and breast-feeding, the value of modest lipid-lowering from colesevelam during pregnancy is likely minimal and colesevelam, which is category B, is not generally recommended.

Conclusion

Colesevelam is an option for patients who have not achieved their LDL-c and non-HDL-c goals with statin therapy, or who are statin intolerant. Colesevelam is also an option to lower both LDL-c and glucose levels in patients with inadequately controlled diabetes. Monotherapy with colesevelam reduces LDL-c by 9%–20% and in combination with statins, produces an additional decrease in mean serum LDL-c of 6%–16%. Although cardiovascular outcomes trials have not been performed for colesevelam, older bile acid sequestrants have been shown to reduce coronary heart disease risk. Triglycerides should be monitored in patients receiving colesevelam since moderate and occasionally severe elevations may occur, especially when triglycerides are >200 mg/dl. Colesevelam is contraindicated in those with triglycerides >400 mg/dl and significant bowel motility disorders.

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