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Department of Vermont Health Access

Therapeutic Class Review
Bile Acid Sequestrants

Overview/Summary

There are several classes of medications used to alter lipids including the hydroxymethylglutaryl coenzyme A reductase inhibitors (statins), fibric acid derivatives, bile acid sequestrants and nicotinic acid (niacin). Each medication class differs with respect to the mechanism by which they alter lipids, as well as to what degree; therefore, Food and Drug Administration (FDA) approved indications for a particular medication class are influenced by the underlying lipid abnormality.

Cholesterol is a fat-like substance (lipid) that is present in cell membranes and is a precursor of bile acids as well as steroid hormones.[1] The bile acid sequestrants work to modify lipids by binding to bile acids in the intestine through anion exchange, which ultimately causes an interruption of their reabsorption. This reduction leads to feedback regulation to increase the conversion of cholesterol to bile acids. The major action of these agents is to reduce low density lipoprotein cholesterol (LDL-C) specifically. Furthermore, the overall reduction in cholesterol causes intrahepatic cholesterol to be reduced which in turn enhances LDL receptor expression. The receptors then bind LDL from the plasma causing a further reduction in blood cholesterol.[1,2] Through a different mechanism, the bile acid sequestrants cause a minimal increase in high density lipoprotein cholesterol.[2]

Use of bile acid sequestrants is effective in patients with mild to moderate elevations of LDL-C.[1,2] When administered as monotherapy these agents have the potential to reduce LDL-C by 10 to 24%, depending on the dose administered.[2] Bile acid sequestrants are also effective as add on therapy in patients with markedly elevated LDL-C who are already receiving a statin or niacin.[1,2] In this instance, doubling the dose of the statin has the potential to further reduce LDL-C by six percent, while adding a moderate dose of a bile acid sequestrant to a statin can potentially produce a 12 to 16% further reduction in LDL-C. Of note, these agents tend to increase triglyceride (TG) levels; therefore, they are contraindicated as monotherapy in patients with high TG levels and in familial dysbetalipoproteinemia.[1]

There are three bile acid sequestrants available: cholestyramine (Prevalite®, Questran®, Questran Light®), colesevelam (Welchol®) and colestipol (Colestid®, Flavored Colestid®). Cholestyramine and colestipol are both available as powders to be mixed with water or juice, and are typically administered once or twice daily with meals.[3-5] Colestipol is also available as a tablet (Colestid®), and the powder formulation is available in two flavors: tasteless (Colestid®) and orange flavored (Flavored Colestid®).[5,6] Colesevelam is available as a powder and as a tablet, and is also typically administered once or twice daily.[7] Colesevelam is more potent compared to either cholestyramine or colestipol.[1] In addition, colesevelam may be more easily administered and better tolerated compared to the other agents.[1,2] All bile acid sequestrants are available generically, with the exception of colesevelam (Welchol®).

The specific FDA approved indications of the various bile acid sequestrants are outlined in Table 2. In general, all of the agents are FDA approved for adjunct treatment in patients with hypercholesterolemia.[3-7] Cholestyramine is also FDA approved for relief of pruritis associated with partial biliary obstruction.[3,4] Colesevelam also has additional FDA approved indications for use as monotherapy in children 10 to 17 years of age for the treatment of heterozygous familial hypercholesterolemia, and as adjunct therapy to diet and exercise to improve glycemic control in adults with type 2 diabetes.[7]

In general, therapeutic lifestyle changes, including diet, exercise and smoking cessation, remain an essential modality in the management of patients with hypercholesterolemia.[1,8,9] When LDL lowering is required, initial treatment with a statin, a bile acid sequestrant or niacin is recommended.[1] However, in general, the statins are considered first line therapy for decreasing LDL-C levels.[1,8-10] If after six weeks of therapy lipid goals are not achieved on a statin alone, a dosage increase or the addition of a bile acid sequestrant or niacin should be considered.[1] Statins are also considered first line in the treatment of heterozygous familial hypercholesterolemia, but if required a bile acid sequestrant can be added to therapy.[8] In addition, the bile acid sequestrants are recognized as the therapy of choice for the management of pruritis associated with primary biliary cirrhosis.[11]

With regards to the use of bile acid sequestrants in the management of patients with diabetes, the Association of Clinical Endocrinologists/American College of Endocrinology notes that colesevelam, reduces blood glucose levels in patient with type 2 diabetes, especially in patients not adequately controlled with metformin, a sulfonylurea or insulin.[12] In general, the American Diabetes Association recommends that a statin be added to lifestyle therapy, regardless of baseline lipid levels, in patients with diabetes. If lipid targets are not achieved with a statin alone, combination therapy with other lipid lowering agents should be considered.[13]

Medications

Table 1. Medications Included Within Class Review

Generic Name (Trade name)	Medication Class	Generic Availability
Cholestyramine (Prevalite®*, Questran®*, Questran Light®*)	Bile acid sequestrants	✔
Colesevelam (Welchol®)	Bile acid sequestrants	-
Colestipol (Colestid®*, Flavored Colestid®*)	Bile acid sequestrants	✔

*Generic available in at least one dosage form and/or strength.

Indications

Table 2. Food and Drug Administration (FDA) Approved Indications[3-7]

Indication	Cholestyramine	Colesevelam	Colestipol
Adjunctive therapy to diet for the reduction of elevated serum cholesterol in patients with primary hypercholesterolemia who do not respond adequately to diet*	✔		✔ †
Adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes		✔	
Adjunct to diet and exercise to reduce elevated low density lipoprotein cholesterol levels in adults with primary hyperlipidemia as monotherapy or in combination with a statin		✔	
Monotherapy or in combination with a statin to reduce low density lipoprotein cholesterol levels in boys and postmenarchal girls, 10 to 17 years of age, with heterozygous familial hypercholesterolemia‡		✔	
Relief of pruritis associated with partial biliary obstruction§	✔		

*May be useful to lower low density lipoprotein cholesterol (LDL-C) levels in patients who also have hypertriglyceridemia, but it is not indicated where hypertriglyceridemia is the abnormality of most concern.
†For the reduction of elevated serum total cholesterol and LDL-C.
‡If after an adequate trial of diet therapy the following findings are present: LDL-C remains ≥190 mg/dL or LDL-C remains ≥160 mg/dL and there is a positive family history of premature cardiovascular disease or two or more other cardiovascular disease risk factors are present in the pediatric patient.
§Has been shown to have a variable effect on serum cholesterol in these patients. Patients with primary biliary cirrhosis may exhibit elevated cholesterol as part of their disease.

In addition to their Food and Drug Administration approved indications, the bile acid sequestrants have the potential to be used off-label in several different clinical situations. Cholestyramine has the potential of being used off-label for the treatment of bile acid malabsorption syndrome, heterozygous familial hypercholesterolemia and generalized atherosclerosis. Colesevelam and colestipol have the potential to be used off-label for the treatment of familial hypercholesterolemia, while colestipol may also be used off-label for the treatment of generalized atherosclerosis.[14]

Pharmacokinetics

Table 3. Pharmacokinetics[14]

Generic Name	Bioavailability (%)	Renal Elimination (%)	Active Metabolites	Half-Life (hours)
Cholestyramine	Not reported	Not reported	Not reported	Not reported
Colesevelam	0	0.05	Not reported	Not reported
Colestipol	0	0.05	Not reported	Not reported

Clinical Trials

Clinical trials demonstrating the safety and efficacy of the bile acid sequestrants in their Food and Drug Administration approved indications are outlined in Table 4.[15-37] In general, the bile acid sequestrants consistently demonstrated "superiority" over placebo in the management of hyperlidpidemia.[16-25] In line with current clinical guidelines, results also demonstrated that the addition of a bile acid sequestrant to another lipid lowering agent has the potential to produce further reductions in low density lipoprotein cholesterol levels compared to monotherapy with either of the agents.[20-27]

The Lipid Research Clinical Coronary Primary Prevention trial demonstrated that compared to placebo, treatment with cholestyramine reduced the risk of coronary heart disease death and/or nonfatal myocardial infarction in asymptomatic males with primary hypercholesterolemia ($P<0.05$).[28,29]

Several clinical trials have demonstrated the safety and efficacy of colesevelam as adjunct therapy in adults with type 2 diabetes. In all of the trials, patients were receiving background therapy with established oral antidiabetic agents.[30-37] Compared to placebo, the addition of colesevelam resulted in significant reductions in glycosylated hemoglobin (HbA_{1c}) levels.[31-36] A trial comparing add on therapy with either colesevelam, rosiglitazone or sitagliptin in type 2 diabetics inadequately controlled on a stable metformin regimen, demonstrated that least squares mean reductions in HbA_{1c} levels from baseline for each treatment were comparable (-0.3 [$P<0.031$], -0.6 [$P<0.001$] and -0.4% [$P<0.008$]). In this trial, after 16 weeks of treatment, 17.9, 35.2 and 27.3% of patients receiving colesevelam, rosiglitazone and sitagliptin achieved a HbA_{1c} <7.0% (*P* values not reported).[37]

Table 4. Clinical Trials

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Hypercholesterolemia				
Davidson et al[15] Colesevelam 0.75 g BID, titrated up to a maximum of 1.875 g BID If a 15 to 30% LDL-C reduction was not achieved with the maxiumum colesevelam dose by week 12, low dose statin or niacin therapy could be added.	ES, OL Patients ≥18 years of age with primary hyper-cholesterolemia (LDL-C ≥160 mg/dL and TG ≤300 mg/dL)	N=260 50 weeks	Primary: Mean change from baseline in LDL-C Secondary: Mean percent change from baseline in LDL-C; mean change and mean percent change from baseline in TC, TG and HDL-C; safety	Primary: Colesevelam monotherapy or combination therapy resulted in significant mean LDL-C level reduction of 29.6 mg/dL (from 185.8 to 156.2 mg/dL), corresponding to a mean 15.0% reduction from baseline (*P*<0.00 for both). Secondary: Colesevelam reduced the mean TC level from baseline to week 50 (270.2 to 258.3 mg/dL) by 11.9 mg/dL (4.0%; *P*<0.001). The median TG level increased from baseline to week 50 (145.5 to 165.0 mg/dL) by 13.0 mg/dL (10.3%). The median HDL-C level increased from baseline to week 50 (49.5 to 54.0 mg/dL) by 5.0 mg/dL (10.8%; *P*<0.001). Twenty three patients discontinued colesevelam due to treatment-emergent adverse events. Treatment-emergent adverse events were reported by 225 patients (86.5%), with the majority of adverse events (74.7%) classified as mild to moderate in severity. The most common adverse events included infection (28.5%), constipation (16.5%), flatulence (13.5%) and general pain (13.1%).
Stein et al[16] Colesevelam vs placebo Period 1 (week -4 to day 0): diet and placebo run in period. Period 2 (day 1 to week 8): DB treatment of colesevelam 1.875 or 3.75 g/day vs placebo.	DB, MC, PC, PG, RCT Patients 10 to 17 years of age with a diagnosis of heterozygous familial hyper-cholesterolemia with a LDL-C >160 mg/dL on a stable NCEP diet for ≥4 weeks and naïve to lipid lowering therapy or LDL-C >130 mg/dL on a	N=194 32 weeks	Primary: Percent change from baseline to week eight in LDL-C Secondary: Percent change in LDL-C from week eight to week 26 and from baseline to week 26; percent change in TC, non-HDL-C, TG, HDL-C, apo A-I and apo B	Primary: Colesevelam 3.75 and 1.875 g/day resulted in a significant mean treatment difference in LDL-C of -12.5 (*P*<0.001) and -6.3% (*P*=0.031), respectively, compared to placebo at week eight. Secondary: During OL treatment of colesevelam, the mean change in LDL-C was -9.3% (*P*<0.001) from week eight to 26. Patients who received placebo during the DB period had the greatest change in mean LDL-C (-14.5%; *P*<0.001), followed by patients receiving colesevelam 1.875 g/day (-11.6%; *P*<0.001) and 3.75 g/day (-1.9%; *P*=0.482). Treatment with colesevelam 3.75 g/day also resulted in a significant mean treatment difference in TC (-7.4%; *P*=0.001), non-HDL-C (-10.9%; *P*=0.0001), apo B (-8.3%; *P*=0.0009), HDL-C (6.1%; *P*=0.008) and apo A-I (6.9%; *P*=0.006) at week eight. There was a nonsignificant median increase

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Period 3 (week 8 to week 26): OL safety evaluation of colesevelam 3.75 g/day.	stable NCEP diet for ≥6 weeks plus a statin and ≥1 of the following: history/presence in patients/first-degree relative of tendinous xanthoma or premature corneal arcus; first-degree adult relative/ biologic offspring with a mutation in the LDL receptor or apo B gene; the presence of untreated LDL-C >190 mg/dL in a first-degree adult relative or the presence of LDL-C >160 mg/dL in siblings <18 years of age and/or a first-degree relative with premature CAD or sudden death from natural causes before 55 (males) or 60 years of age (females)		from baseline to week eight, week eight to week 26 and from baseline to week 26; percentage of patients achieving LDL-C <110 mg/dL	in TG (5.1%; *P*=0.466) at week eight compared to placebo. Over the entire treatment period, treatment with colesevelam 3.75 g/day resulted in a mean reduction from baseline in LDL-C of -14.0% (*P*<0.001) across all patients. Colesevelam 3.75 g/day also achieved clinically significant mean reductions from baseline in TC (-8.0%; *P*<0.001), non-HDL-C (-11.3%; *P*<0.001) and apo B (-11.3%; *P*<0.001); clinically significant increases from baseline in mean HDL-C (8.1%; *P*<0.001) and apo A-I (5.6%; *P*<0.001) and a significant median increase in TG (11.5%; *P*<0.001). Seven patients (3.7%) achieved the goal of LDL-C <110 mg/dL during period 2; five were receiving colesevelam 3.75 g/day and two were receiving colesevelam 1.875 g/day. Of the seven patients, two were statin naïve and five were taking a statin.
Rosenson et al[17] Colesevelam 1.5 to 3.75 g/day	DB, MC, PC, RCT Adults with hyper-cholesterolemia (LDL-C >160 mg/dL)	N=137 6 weeks	Primary: LDL particle size and number Secondary:	Primary: Mean LDL particle size increased significantly with colesevelam 3.75 g/day (*P*=0.01). Mean LDL particle number decreased significantly by 13.7% with

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vs placebo			Not reported	colesevelam 3.75 g/day (*P*=0.0002). Mean LDL particle number decreased significantly by 6.8% with colesevelam 3.0 g/day (*P*=0.03). Secondary: Not reported
Bays et al[18] Colesevelam 3.75 g/day vs placebo	MA of 3 DB, MC, PC, PG, RCTs Patients ≥18 years of age with a LDL-C 100 to 250 mg/dL, TG ≤300 mg/dL and on stable doses of statin therapy (atorvastatin, pravastatin or simvastatin) for ≥4 weeks	N=204 6 weeks	Primary: Mean percent change from baseline in LDL-C Secondary: hsCRP; absolute and percent change in HDL-C, TC, apo A-I, apo B and TG; absolute change in hsCRP; safety	Primary: Colesevelam achieved significantly greater reductions in LDL-C compared to placebo (*P*<0.01 for absolute difference; *P*≤0.001 for percent treatment difference). Secondary: hsCRP levels decreased significantly when compared to placebo when colesevelam was combined with simvastatin or pravastatin (*P*=0.0154 and *P*=0.0279, respectively). Colesevelam did not achieve a significant increase in HDL-C compared to placebo (*P*>0.05). Colesevelam achieved significantly greater reductions in TC compared to placebo (*P*<0.05). Apo B concentrations were not significantly different between treatment groups (*P* value not reported). No serious drug-related adverse events were reported. The incidence of drug-related adverse events was higher with colesevelam (13 to 26%) compared to placebo (0 to 13%; *P* value not reported).
Insull et al[19] Colesevelam 2.3 to 4.5 g/day vs	DB, MC, PC, RCT Patients with primary hyper-cholesterolemia (LDL-C 130 to 220 mg/dL)	N=467 32 weeks (8 weeks of diet lead in plus 24 weeks of DB	Primary: Mean absolute change from baseline in LDL-C Secondary: Mean percent	Primary: All doses of colesevelam resulted in significant absolute and percent change decreases in LDL-C at the end point as compared to placebo (*P*<0.001 for all). Absolute change and percent decreases in LDL-C for the 2.3, 3.0, 3.8 and 4.5 g doses were 14 (9%), 19 (12%), 24 (15%) and 28 mg/dL (18%) (*P* values not reported).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
placebo		treatment)	change in LDL-C; mean absolute and percent change in TC, apo B and apo A-I; median absolute change and percent change in HDL-C and TG	Secondary: All doses of colesevelam resulted in significant reductions of TC (*P*<0.001). Absolute change and percent decreases in TC for the 2.3, 3.0, 3.8 and 4.5 g doses were 10 (4%), 15 (6%), 18 (7%) and 24 mg/dL (10%) (*P* values not reported). All doses of colesevelam resulted in significant increases in HDL-C (*P*<0.001). Absolute change and percent increases in HDL-C for the 2.3, 3.0, 3.8 and 4.5 g doses were 2 (3%), 2 (4%), 2 (3%) and 2 mg/dL (3%) (*P* values not reported). All doses of colesevelam resulted in significant reductions in apo B relative to baseline (*P*<0.001). Changes in apo A-I did not result in significant changes relative to baseline, except the 2.3 and 3.0 g doses resulted in significant changes in apo A-I (*P*=0.02 and 0.03, respectively) TG levels did not change significantly as compared to placebo; however, increases of 5 to 10% were observed within groups from baseline to end point (*P*<0.05).
Huijgen et al[20] Colesevelam 3,750 mg/day vs placebo All patients were receiving ezetimibe/simvastatin.	DB, PC, RCT Patients 18 to 75 years of age with familial hyper-cholesterolemia refractory to treatment	N=86 12 weeks	Primary: Percent change from baseline to week six in LDL-C Secondary: Percentage change from weeks six to 12 in HDL-C, TC, TG, apo A1, apo B, apo B/A1; percentage change from baseline to week	Primary: The between-group difference in change from baseline LDL-C was significant at week six, with an LSM change of -18.5% (95% CI, -25.3 to -11.8) Secondary: Between group differences (95% CI) in LDL-C, TC, HDL-C, TG and apo B/A1 after 12 weeks were -12.0 (-17.8 to -6.3), -7.3 (-12.0 to -2.6), 3.3 (-2.4 to 9.0), 2.8 (-10.4 to 15.9) and -12.2% (-20.2 to -4.2). Mean TC concentrations were significantly reduced with colesevelam compared to placebo at weeks six and 12 (LSM between-group differences, -11.1 and -7.3%; *P*<0.001 and *P*<0.003). On average, TG levels increased with colesevelam from baseline to weeks six and 12. There was no significant group differences in HDL-C at week six and 12 (*P* values not reported).

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			12 in LDL-C; proportion of patients achieving an LDL-C target of ≤2.5 mmol/L at weeks six and 12; proportion of patients with a decrease from baseline in LDL-C ≥15% at weeks six and 12; absolute changes in fasting glucose, HbA_{1c}, and hsCRP at weeks six and 12	The difference in the proportions of patients who achieved the target LDL-C (≤2.5 mmol/L) with colesevelam and placebo was not significant (9 vs 3%; *P* value not reported). The proportion of patients who achieved ≥15% reduction in LDL-C at week six was significantly higher with colesevelam (32 vs 0%; *P*<0.001). This difference remained significant at week 12 (30 vs 8%; *P*=0.012). Although not significant at week six (-0.06%), the LSM between-group difference in change from baseline to week 12 in mean HbA_{1c} concentration was significant (-0.12%; *P*=0.027). There were no significant between-group differences in fasting glucose or hsCRP at week six and 12.
Blankernhorn et al[21] Colestipol 30 g/day plus niacin 3 to 12 g/day vs placebo	DB, PC, RCT Nonsmoking men 49 to 59 years of age with progressive atherosclerosis who had coronary bypass surgery not involving valve replacement performed ≥3 months prior and a fasting blood cholesterol level 185 to 350 mg/dL	N=188 2 years	Primary: Coronary global change score Secondary: Change from baseline in lipid parameters	Primary: Deterioration in overall coronary status was significantly less with combination therapy compared to placebo (*P*<0.001). Atherosclerosis regression, as indicated by perceptible improvement in overall coronary status, occurred in 16.2 and 2.4% of patients receiving combination therapy and placebo (*P*=0.002). Combination therapy resulted in a significant reduction in the average number of lesions per patient that progressed (*P*<0.03) and the percentage of patients with new atheroma formation in native coronary arteries (*P*<0.03). The percentage of patients receiving combination therapy with new lesions (*P*<0.04) or any adverse change in bypass grafts (*P*<0.03) was significant reduced. Secondary: Large, significant decreases in TC (26 vs 4%), TG (22 vs 5%), LDL-C (43 vs 5%) and LDL-C/HDL-C (57 vs 6%), and a large, significant increase in HDL-C (37 vs 2%) were achieved with combination therapy compared to

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				placebo (*P*<0.001 for all). Modifications in lipid parameters achieved with combination therapy were significant compared to baseline values (*P* values not reported).
Brown et al[22] Colestipol 5 to 10 g TID plus niacin 125 mg BID, titrated to 1 to 1.5 g TID vs Colestipol 5 to 10 g TID plus lovastatin 20 mg BID, titrated to 40 mg BID vs placebo (or colestipol if LDL-C was elevated)	DB, PC, RCT Men ≤62 years of age with elevated apo B and a family history of CAD	N=120 32 months	Primary: Average change in the percent stenosis for the worst lesion in each of the nine proximal segments Secondary: Average changes in all lesions measured in each patient and in proximal lesions causing ≥50% (severe) stenosis or <50% (mild) stenosis at baseline	Primary: On average, placebo (conventional therapy) increased the index of stenosis by 2.1 percentage points from a baseline of 34%. By contrast, it decreased by 0.7 percentage points with colestipol plus lovastatin and by 0.9 percentage points with colestipol and niacin (*P*<0.003 for trend). At trial end, on average, these nine lesions were almost three percentage points less severe among patients treated intensively compared to conventionally. This difference represents almost 1/10 of the amount of disease present at baseline (34% stenosis). Secondary: Placebo (conventional therapy) resulted in consistent worsening of disease when looking at the effect of treatment on certain subsets of lesions (all lesions measured in each patient, lesions causing severe or mild stenosis and those that did not cause total occlusion at baseline). The results with both treatment groups were significantly different from those receiving conventional therapy for each subset, demonstrating either a mean regression or no change in severity of disease.
Hunninghake et al[23] Colesevelam 3.8 g/day vs atorvastatin 10 mg/day vs colesevelam 3.8 g/day plus atorvastatin 10 mg/day	DB, MC, PC, RCT Patients with LDL-C ≥160 mg/dL and TG ≤300 mg/dL	N=91 4 weeks	Primary: Change from baseline in LDL-C Secondary: Change from baseline in TC, HDL-C, TG, apo B, apo A-I and lipoprotein	Primary: All treatments resulted in significant LDL-C reductions as compared to baseline. LDL-C reductions from baseline were -12% with colesevelam (*P*<0.05), -38% with atorvastatin 10 mg (*P*<0.0001), -48% with colesevelam plus atorvastatin (*P*<0.0001) and -53% with atorvastatin 80 mg (*P*<0.0001), respectively. Secondary: Colesevelam reduced TC by 6% (*P*<0.05), increased HDL-C by 3% (*P*<0.05) and increased TG by 10% (*P* value not reported). Atorvastatin 10 mg reduced TC by 27% (*P*<0.0001), increased HDL-C by 8% (*P*<0.05) and reduced TG by 24% (*P*<0.05).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vs atorvastatin 80 mg/day vs placebo				Colesevelam plus atorvastatin reduced TC by 31% (*P*<0.0001), increased HDL-C by 11% (*P*<0.05) and reduced TG by 1% (*P* value not reported). Atorvastatin 80 mg reduced TC by 39% (*P*<0.0001), increased HDL-C by 5% (*P*<0.05) and reduced TG by 33% (*P*<0.0001). Reductions in TC were significant between all treatment groups except atorvastatin 10 mg relative to colesevelam plus atorvastatin. No significant differences in HDL-C were found between the treatment groups (*P* values not reported). Apo B levels decreased significantly for with all treatments relative to baseline (*P*<0.01). No significant changes in apo A-I and lipoprotein were reported (*P* values not reported).
Davidson et al (abstract)[24] Colesevelam 2.3 g/day vs lovastatin 10 mg/day vs colesevelam 2.3 g/day plus lovastatin 10 mg/day administered together vs colesevelam 2.3 g/day plus lovastatin 10 mg/day administered apart vs placebo	DB, MC, PC, RCT Patients with an elevated LDL-C level	N=135 4 week	Primary: Percent change from baseline in LDL-C Secondary: Changes in TC, HDL-C, TG and apo B	Primary: Colesevelam plus lovastatin administered together significantly reduced LDL-C by 34% (-60 mg/dL; *P*<0.0001). Colesevelam plus lovastatin administered apart significantly reduced LDL-C by 32% (-53 mg/dL; *P*<0.0001). Lovastatin reduced LDL-C by 22% (-39 mg/dL; *P* value not reported). Colesevelam reduced LDL-C by 7% (-13 mg/dL; *P* value not reported). Colesevelam plus lovastatin administered together or apart were more effective than either treatment alone (*P*<0.05). Secondary: Colesevelam plus lovastatin administered together or apart resulted in significant reductions in TC by 21% and apo B by 24% (*P*<0.0001 for each). No significant effect on HDL-C or TG was observed for either of the combination treatments (*P* value not reported).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Knapp et al[25] Colesevelam 3.8 g/day vs simvastatin 10 mg/day vs colesevelam 3.8 g/day plus simvastatin 10 mg/day vs colesevelam 2.3 g/day vs simvastatin 20 mg/day vs colesevelam 2.3 g/day plus simvastatin 20 mg/day vs placebo	DB, MC, PC, RCT Patients ≥18 years of age with LDL-C ≥160 mg/dL and TG ≤300 mg/dL who are not taking cholesterol lowering medication	N=258 6 weeks	Primary: Change from baseline in LDL-C Secondary: Percent change in LDL-C; mean and percent change from baseline in TC, HDL-C, TG, apo B and apo A-I	Primary: LDL-C changes from baseline were -7 mg/dL with placebo (*P*<0.05), -31 mg/dL with colesevelam 3.8 g (*P*<0.0001), -48 mg/dL with simvastatin 10 mg (*P*<0.0001), -80 mg/dL with colesevelam 3.8 g plus simvastatin 10 mg (*P*<0.0001), -17 mg/dL with colesevelam 2.3 g (*P*<0.0001), -61 mg/dL with simvastatin 20 mg (*P*<0.0001) and -80 mg/dL with colesevelam 2.3 g plus simvastatin 20 mg (*P*<0.0001), respectively. Secondary: LDL-C percent changes from baseline were -4% with placebo (*P*<0.05), -16% with colesevelam 3.8 g (*P*<0.0001), -26% with simvastatin 10 mg (*P*<0.0001), -42% with colesevelam 3.8 g plus simvastatin 10 mg (*P*<0.0001), -8% with colesevelam 2.3 g (*P*<0.0001), -34% with simvastatin 20 mg (*P*<0.0001) and -42% with colesevelam 2.3 g plus simvastatin 20 mg (*P*<0.0001), respectively. Significant changes from baseline were observed for all treatments in mean and percent change in TC (*P*<0.0001 for all, except colesevelam 2.3 g; *P*<0.05). Significant changes from baseline were observed for mean and percent change in HDL-C with simvastatin 10 mg (*P*<0.05), colesevelam 3.8 g plus simvastatin 10 mg (*P*<0.0001), colesevelam 2.3 g (*P*<0.05), simvastatin 20 mg (*P*<0.05) and colesevelam 2.3 g plus simvastatin 20 mg (*P*<0.05). Significant changes from baseline were observed for mean and percent change in TG with colesevelam 3.8 g (*P*<0.05), simvastatin 10 mg (*P*<0.05), simvastatin 20 mg (*P*<0.05) and colesevelam 2.3 g plus simvastatin 20 mg (*P*<0.05). Significant reductions from baseline for apo B were observed with all treatments. Reductions were significant (*P*<0.05) compared to placebo for all treatments except colesevelam 2.3 g (*P* value not reported). Significant increases in apo A-I were achieved with all treatments except simvastatin 10 mg (*P*<0.05).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Eriksson et al[26] Cholestyramine 16 g/day vs cholestyramine 8 g/day plus pravastatin 20 mg/day vs pravastatin 20 mg/day vs pravastatin 40 mg/day	MC, RCT Patients 30 to 65 years of age	N=2,036 12 months	Primary: Percent change from baseline in LDL-C Secondary: Compliance	Primary: Percent changes in LDL-C from baseline to end point with cholestyramine, cholestyramine plus pravastatin, pravastatin 20 mg and pravastatin 40 mg were -26 (95% CI, -23 to -29), -36 (95% CI, -33 to -39), -27 (95% CI, -25 to -29) and -32% (95% CI, -30 to -34). Secondary: Compliance rates with cholestyramine, cholestyramine plus pravastatin, pravastatin 20 mg and pravastatin 40 mg were 44, 53, 76 and 78% (*P* values not reported) Pravastatin adverse events were the most common reasons for withdrawal. Adverse events were most common with cholestyramine and cholestyramine plus pravastatin.
Ballantyne et al[27] Rosuvastatin 80 mg/day vs rosuvastatin 80 mg/day plus cholestyramine 16 g/day All patients received rosuvastatin 40 mg/day for a 6 week run in period.	MC, OL, PG, RCT Patients ≥18 years of age with severe hyper-cholesterolemia (LDL-C 190 to 400 mg/dL) and fasting TG <400 mg/dL	N=147 12 weeks	Primary: Percent change from baseline in LDL-C Secondary: Percent change from baseline in LDL-C after six weeks of 40 mg rosuvastatin; percent change from baseline at six and 12 weeks of rosuvastatin treatment for TC, HDL-C, TG, apo A-I, apo B, lipid ratios (LDL:HDL) and inflammatory	Primary: At 12 weeks, no significant difference between the treatment groups was observed; rosuvastatin achieved a LDL-C reduction of 56.4% and rosuvastatin plus cholestyramine achieved a reduction of 60.5% ($P<0.08$). Secondary: LDL-C reductions were 52.2% after treatment with rosuvastatin 40 mg. Changes in TC ($P=0.20$), HDL-C ($P=0.71$), TG ($P=0.47$), apo B ($P=0.75$), apo A-I ($P=0.53$) and lipid ratios ($P=0.17$) were not significantly different between the treatment groups. Decreases in CRP were 29% after six weeks of treatment, 42% with rosuvastatin 80 mg and 48% with rosuvastatin 80 mg plus cholestyramine (*P* value not reported). Forty nine percent of patients receiving cholestyramine were not compliant with the treatment.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
			markers (CRP, IL6); compliance	
Hypercholesterolemia Clinical Outcomes Trials				
No authors listed[28,29] The Lipid Research Clinics Coronary Primary Prevention Trial Cholestyramine vs placebo	DB, MC, RCT Asymptomatic males with primary hyper-cholesterolemia following a moderate cholesterol lowering diet	N=3,806 7.4 years (average)	Primary: CHD death and/or nonfatal MI Secondary: Changes in TC and LDL-C; incidence rates of positive stress tests, angina and coronary bypass surgery	Primary: Cholestyramine was associated with a 19% reduction in risk of CHD death or nonfatal MI ($P<0.05$). Secondary: Cholestyramine achieved reductions in TC and LDL-C of 13.4 and 20.3% compared to 4.9 and 7.7% with placebo (*P* values not reported). Incidence rates of positive stress tests, angina and coronary bypass surgery were decreased with cholestyramine by 25, 20 and 21%, respectively (*P* values not reported).
Type 2 Diabetes				
Goldfine et al[30] Colesevelam 3.75 g/day	ES, OL Patients who completed 1 of 3 DB RCTs wherein colesevelam was added to insulin-, metformin- and sulfonylurea-based therapies	N=509 52 weeks	Primary: Safety and tolerability Secondary: Change from baseline in HbA_{1c} and FPG, percent change in lipid and lipoprotein levels, change in lipid ratios, percentage of patients who achieved HbA_{1c} <7% at week 52	Primary: In total, 361 patients (70.9%) experienced an adverse event during the ES phase. The majority of adverse events (88.1%) were mild to moderate in severity. Fifty six patients (11.0%) experienced a drug-related adverse event that was gastrointestinal in nature. In general, the incidence of drug-related adverse events was greater in patients who received placebo in the DB phase relative to those who had received colesevelam. Thirty five patients (6.9%) discontinued due to an adverse event. Sixteen patients (3.1%) discontinued due to a drug-related adverse event. Fifty four patients (10.6%) had a serious adverse event; only one serious adverse event was considered by the investigator to be drug-related. Twelve patients (2.4%) discontinued treatment due to a serious adverse event. Two patients died during the trial (MI and pulmonary embolism); both events were considered by the investigator to be unrelated to colesevelam. Secondary: An overall reduction in mean HbA_{1c} was maintained in patients who received colesevelam during the DB phase and continued on this treatment during the OL, ES phase. After 68 to 78 total weeks of colesevelam treatment there was an overall reduction in HbA_{1c} of 0.3% from baseline.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				In general, findings for FPG were consistent with observed effects on HbA_{1c}. Improvements in mean LDL-C levels achieved with colesevelam during the DB phases were maintained, and in both the patients who received colesevelam for 68 to 78 weeks and those that received colesevelam for 52 weeks, effects were sustained over the 52 week ES phase. At week 52, lipid and lipoprotein levels were similar between the group that received colesevelam for the entire treatment period and those who originally received placebo. At week 52, 72 patients (14.1%) achieved HbA_{1c} <7% and 137 patients (26.9%) achieved a reduction in HbA_{1c} ≥0.7% from baseline. Similarly, 126 patients (24.8%) achieved a reduction in FPG ≥30 mg/dL from baseline at week 52,
Zieve et al[31] GLOWS Colesevelam 3.75 g/day vs placebo	DB, PC, PG, PRO, RCT Patients with type 2 diabetes, an HbA_{1c} 7 to 10% and on a stable dose of a sulfonylurea and/or metformin as their only antidiabetic agent for ≥90 days	N=65 12 weeks	Primary: Change from baseline in HbA_{1c} Secondary: Changes in fructosamine, FPG, postprandial glucose and meal glucose response (difference between pre and postprandial glucose levels); percent change in lipids (LDL-C, TC, TG, apo A-I and apo B)	Primary: The change from baseline in HbA_{1c} with colesevelam and placebo was -0.3 and 0.2%, for a treatment difference of 0.5% (*P*=0.007). For patients with a baseline HbA_{1c} ≥8, there was a greater difference in HbA_{1c} (-1%) after 12 weeks of treatment (*P*=0.002). The reduction in HbA_{1c} in the treatment groups did not differ based on oral antidiabetic treatment (*P* value not reported). Secondary: Significantly lower fructosamine levels were observed with colesevelam at week 12 (*P*=0.011). Significantly lower FPG levels were observed with colesevelam at weeks four (*P*=0.016) and eight (*P*=0.011), but not at week 12 (*P* value not reported). Significantly lower postprandial glucose levels were observed with colesevelam at week 12 (*P*=0.026). No significant difference between the treatment groups was observed in

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				meal glucose response (*P*=0.195). Significantly lower lipid parameters, including LDL-C (*P*=0.007), TC (*P*=0.019), apo B (*P*=0.019) and LDL particle concentration (*P*=0.003) were observed with colesevelam compared to placebo, respectively.
Rosenstock et al (abstract)[32] Colesevelam 3.75 g/day vs placebo All patients receieved OL metformin 850 mg/day, titrated at week 2 to 1,700 mg/day.	DB, PC, RCT Adult patients with type 2 diabetes (HbA_{1c} 6.5 to 10.0%) and hyper-cholesterolemia (LDL-C ≥100 mg/dL)	N=286 16 weeks	Primary: Change from baseline in HbA_{1c} Secondary: Change from baseline in LDL-C, TC, non-HDL-C, apo B, hsCRP, apo A-1 and TG; proportion of patients who achieved recommended treatment goals; safety and tolerability	Primary: Mean HbA_{1c} was reduced by 1.1 and 0.8% with colesevelam (from 7.8% at baseline to 6.6% at trial end) and placebo (from 7.5 to 6.7% at trial end), resulting in a treatment difference of -0.3% at trial end (*P*=0.0035). Secondary: Colesevelam significantly reduced LDL-C (-16.3%), TC (-6.1%), non-HDL-C (-8.3%), apo B (-8.0%) and hsCRP (-17%) (*P*<0.01 for all). Colesevelam significantly increased apo A-1 (4.4%) and TG (18.6%) compared to placebo (*P*<0.01 for all). The proportion of patients who achieved recommended goals with colesevelam compared to placebo, respectively, were as follows: HbA_{1c} <7; 67 vs 56% (*P*=0.0092), LDL-C <100 mg/dL; 48 vs 18% (*P*<0.001) and composite HbA_{1c} <7% plus LDL-C <100 mg/dL; 40 vs 12 (*P*<0.001). Safety and tolerability were similar between the two treatment groups.
Bays et al[33] Colesevelam 3.75 g/day vs placebo All patients continued their current antidiabetic treatment regimens. All patients entered a 2 week, SB, placebo run in	DB, MC, PC, PG, RCT Patients 18 to 75 years of age with type 2 diabetes with inadequate glycemic control (HbA_{1c} 7.5 to 9.5%), taking a stable dose (≥90 days) of metformin monotherapy or metformin in combination with	N=316 26 weeks	Primary: Change from baseline in HbA_{1c} Secondary: Mean change in HbA_{1c}, FPG and fructosamine levels from baseline to weeks six, 12, 18 and 26 for metformin monotherapy or combination	Primary: Colesevelam reduced LSM HbA_{1c} level by 0.39% compared to 0.15% with placebo, resulting in a significant LSM treatment difference of -0.54% (*P*<0.001). A significant LSM treatment difference was observed beginning at week six (-0.46%; *P*<0.001). Secondary: Mean reductions in HbA_{1c} level when colesevelam was added to either metformin monotherapy or combination therapy were consistent with findings for the total population at week 26 (metformin monotherapy, 0.44 vs 0.02%; LSM treatment difference, -0.47%; *P*=0.002 and metformin combination therapy, -0.35 vs 0.27%; LSM treatment difference, -0.62%; *P*<0.001).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
period.	other oral antidiabetic drugs		therapy; assessment of patients who experienced a predefined reduction in FPG level ≥30 mg/dL or in HbA_{1c} level ≥0.7% from baseline; mean change from baseline in C-peptide, adiponectin, insulin and HOMA index levels; mean change and mean percent change from baseline in TC, LDL-C, HDL-C, non-HDL-C, apo A-I and apo B; mean change from baseline in TC/HDL-C, LDL-C/HDL-C, non-HDL-C/HDL-C and apo B/apo A-I; median change from baseline in hsCRP and TG	Colesevelam reduced FPG level compared to placebo at week 26 (-13.9 mg/dL; *P*=0.01), with a significant LSM treatment difference observed at week six (-20.8 mg/dL; *P*<0.001). Colesevelam reduced fructosamine level compared to placebo (-23.2 μmol/L; *P*<0.001), with a significant LSM treatment difference observed at week six (-25.5 μmol/L; *P*<0.001). In total, 71 (47.7%) and 54 (35.5%) patients receiving colesevelam and placebo experienced either a reduction in FPG level ≥30 mg/dL or in HbA_{1c} level ≥0.7% from baseline at week 26 (*P*=0.03). A significantly greater percentage of patients receiving colesevelam achieved a HbA_{1c} level reduction (38.3 vs 20.4%; *P*<0.001 vs placebo). Compared to placebo, colesevelam did not produce a significant LSM treatment difference for C-peptide level (-0.1 ng/mL; *P*=0.54). Similarly, no differences were observed in adiponectin (-0.3 μg/mL; *P*=0.52), insulin (-0.9 μIU/mL; *P*=0.51) or HOMA index (-0.3; *P*=0.68). Compared to placebo, colesevelam reduced LSM and mean percentage of LDL-C, TC, non-HDL-C and apo B levels at week 26 (*P*<0.001 for all). Compared to placebo, colesevelam was not associated with a significant LSM treatment difference in TG level (8.5 mg/dL; *P*=0.24). Compared to placebo, colesevelam reduced LSM TC/HDL-C, LDL-C/HDL-C, non-HDL-C/HDL-C and apo B/apo A-I ratios at week 26 (*P*<0.003 for all). Compared to placebo, colesevelam resulted in a LSM treatment difference in hsCRP level of -0.40 mg/L (-14.4%; *P*=0.02).
Fonseca et al[34] Colesevelam 3.75 g/day vs	DB, MC, PC, PG, RCT Adult patients with type 2 diabetes who	N=461 26 weeks	Primary: Mean change from baseline in HbA_{1c}	Primary: Colesevelam reduced HbA_{1c} by 0.320±0.066% compared to an increase of 0.230±0.065% with placebo, resulting in a significant LSM treatment difference of -0.540±0.090% (*P*<0.001).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
placebo All patients continued their current antidiabetic treatment regimens. All patients entered a 2 week, SB, placebo run in period.	are inadequately controlled (HbA_{1c} 7.5 to 9.5%) on a stable dose of a sulfonylurea alone or in combination with additional antidiabetic agents for ≥90 days		Secondary: Mean change from baseline in FPG, fructosamine and C-peptide; mean change in HbA_{1c} for sulfonylurea monotherapy and combination therapy; percentage of patients achieving a reduction in FPG level ≥30 mg/dL or in HbA_{1c} level ≥0.7% from baseline; mean change in lipids, lipoproteins and lipid and lipoprotein ratios; median change and percent change in hsCRP and TG	Secondary: A significant LSM treatment difference between colesevelam and placebo in FPG was observed by week 26 (-13.50±5.14 mg/dL; *P*=0.009), with a significant treatment difference observed as early as six weeks (-13.70±3.98 mg/dL; *P*<0.001). Similar results were observed for changes with fructosamine levels (treatment difference, -21.40±4.59 µmol/L; *P*<0.001). No significant difference was observed in C-peptide levels (treatment difference, -0.170±0.101 ng/mL; *P*=0.102). Similar effects in the reduction of HbA_{1c} were observed in sulfonylurea monotherapy (-0.790±0.154%; *P*<0.001) and sulfonylurea combination therapy (-0.420±0.110%; *P*<0.001). A significantly greater percentage of patients receiving colesevelam achieved a HbA_{1c} reduction ≥0.7% compared to placebo (35.2 vs 16.5%; *P*<0.001). In addition, a significantly greater proportion of patients receiving colesevelam achieved either a reduction in HbA_{1c} ≥0.7% or a reduction in FPG ≥30 mg/dL by trial end (47.5 vs 32.1%; *P*=0.001). Significant LSM percent treatment differences in LDL-C, non-HDL-C, TG, TC, apo A-I and apo B were observed with colesevelam compared to placebo (*P*<0.001 for all). Significant LSM treatment differences between colesevelam and placebo were observed in the ratios of TC/HDL-C, LDL-C/HDL-C, non-HDL-C/HDL-C and apo B/apo A-I (*P*≤0.003 for all). There was a nonsignificant LSM treatment difference between colesevelam and placebo in hsCRP levels (*P*=0.063).
Goldberg et al[35] Colesevelam 3.75 g/day vs placebo	DB, MC, PC, PG, PRO, RCT Patients 18 to 75 years of age with type 2 diabetes inadequately	N=287 16 weeks	Primary: Mean change from baseline in HbA_{1c} Secondary: Mean change in	Primary: LSM change in HbA_{1c} level from baseline at week 16 was -0.41 and 0.09% with colesevelam and placebo, resulting in a treatment difference of -0.50% (*P*<0.001) Secondary: A numerically greater reduction in FPG level from baseline to week 16 was

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
All patients entered a 2 week, SB, placebo run-in period.	controlled (HbA_{1c} 7.5 to 9.5%) with insulin alone or in combination with oral antidiabetic agents, receiving a stable dose of insulin for ≥6 weeks and a C-peptide >0.5 ng/mL, LDL-C ≥60 mg/dL and TG ≤500 mg/dL		FPG and fructosamine from baseline to weeks four, eight and 16; arbitrary predefined assessment of glycemic control response; lipid profile	observed with colesevelam compared to placebo (treatment difference, -14.6 mg/dL; *P*=0.08); however, colesevelam, compared to placebo, significantly reduced FPG level at weeks four, eight and 16 (-15.1, -17.2 and -23.6 mg/dL, respectively; *P* values not reported). Colesevelam significantly reduced mean fructosamine levels from baseline to weeks four, eight and 16 compared to placebo (LSM treatment difference, -21.7 µmol/L; *P*<0.001 at week 16). Seventy (48.6%) and 43 (31.6%) patients receiving colesevelam and placebo had glycemic control response (*P*=0.004). More than twice as many patients receiving colesevelam had a reduction in the HbA_{1c} level ≥0.7% compared to those receiving placebo (34.7 vs 14.0%; *P*<0.001). No significant difference was observed in the percentage of patients achieving a reduction in FPG level ≥30 mg/dL. Colesevelam reduced LDL-C to a significantly greater percentage compared to placebo at week 16 (*P*<0.001). A significant increase in TG was also observed (*P*<0.001). Colesevelam also significantly reduced apo B (*P*=0.04), but did not result in a significant increase in apo A-I after 16 weeks. Colesevelam resulted in a significant decrease in LDL-C/HDL-C and apo B/apo A-I but not in the TC/HDL-C or non-HDL-C/HDL-C ratios (*P* values not reported).
Jialal et al[36] Colesevelam vs placebo All patients recieved their established antidiabetes therapy.	Post-hoc, pooled analysis of 3 RCTs Patients with type 2 diabetes	N=1,018 Not reported	Primary: Glycemic and lipid effects Secondary: Glycemic and lipid effects in colesevelam monotherapy and combination therapy	Primary: By trial end, mean HbA_{1c} was significantly reduced with colesevelam compared to placebo (treatment difference, -0.54%; *P*<0.0001). Mean FPG was significantly reduced with colesevelam compared to placebo (treatment difference, -15.1 mg/dL; *P*<0.0001). Colesevelam achieved significant reductions in both TC and LDL-C compared to placebo (treatment difference, -5.15 and -15.30%; *P*<0.0001). Median TG was significantly increased with colesevelam compared to placebo (treatment difference, 15.0%; *P*<0.0001). Mean non-HDL-C and apo B levels were also significantly reduced with colesevelam compared to placebo (treatment difference, -6.80 and -6.60%; *P*<0.0001). No significant effect was achieved on mean HDL-C levels (treatment difference, 0.02%; *P*

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				value not reported), but mean apo A-I levels increased significantly with colesevelam (treatment difference, 2.8%; *P*<0.0001). Median levels of hsCRP were also signifincatly reduced with colesevelam compared to placebo (treatment difference, -0.4 mg/L; *P*=0.0009). Secondary: The effects of colesevelam that were observed for the total group was similar in those who were receiving colesevelam as monotherapy or as a combination therapy with regard to significant reductions in HbA_{1c} (treatment difference, -0.63 and -0.48%; *P*<0.0001 for both), FPG (-12.7 and -16.8 mg/dL; *P*<0.0001 for both) and LDL-C (-12.9 and -16.8%; *P*<0.0001 for both). For patients receiving colesevelam as monotherapy, median TG levels significantly increased (treatment difference, 12.3%; *P*=0.0013); there was no significant change in TC, non-HDL-C, apo B and hsCRP levels (treatment difference, -4.84%, -6.17%, -4.98% and -0.2 mg/L; *P*=0.003, *P*=0.005, *P*=0.009 and *P* value not reported). For colesevelam as combination therapy, TG levels significantly increased compared to placebo (treatment difference, 16.6%; *P*<0.0001), while TC, non-HDL-C and apo B levels significantly reduced (treatment difference, -5.4, -7.2 and -7.7%; *P*<0.0001 for all). Apo A-I levels significantly increased and hsCRP significantly decreased with colesevelam as combination therapy (treatment difference, 3.4% and -0.5 mg/L; *P*<0.0001 and *P*=0.0027).
Rigby et al (abstract)[37] Colesevelam 3.75 g/day vs rosiglitazone 4 mg/day vs	MC, OL Adult patients with inadequately controlled type 2 diabetes (HbA_{1c} 7 to 10%) on a stable metformin regimen (1,500 to 2,550 mg/day for ≥3	N=169 16 weeks	Primary: Change from baseline in HbA_{1c} Secondary: Change from baseline in LDL-C	Primary: LSM reductions in HbA_{1c} from baseline were -0.3 (*P*<0.031), -0.6 (*P*<0.001) and -0.4% (*P*<0.008) with colesevelam, rosiglitazone and sitagliptin. At trial end, 17.9, 35.2 and 27.3% of patients receiving colesevelam, rosiglitazone and sitagliptin achieved a HbA_{1c} of <7% (*P* values not reported). Secondary: Compared to baseline, colesevelam significantly reduced LDL-C (11.6%),

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
sitagliptin 100 mg/day All patients continued their existing metformin thearpies.	months)			whereas levels were significantly increased with rosiglitazone (7.8%) and sitagliptin (7.7%), respectively. At trial end, 42.3, 23.5 and 24.5% of patients receiving colesevelam, rosiglitazone and sitagliptin achieved an LDL-C of <100 mg/dL (*P* values not reported).

Drug regimen abbreviations: BID=twice daily, TID=three times daily
Study abbreviations: CI=confidence interval, DB=double-blind, ES=extension study, MA=meta-analysis, MC=multicenter, OL=open label, PC=placebo-controlled, PG=parallel group, PRO=prospective, RCT=randomized controlled trial, SB=single-blind
Miscellaneous abbreviations: apo A-1=apolipoprotein A-1, apo B=apolipoprotein B, CAD=coronary artery disease, CHD=coronary heart disease, CRP=C-reactive protein, FPG=fasting plasma glucose, HbA_{1c}=glycosylated hemoglobin, HDL-C=high density lipoprotein cholesterol, hsCRP=high-sensitivity C-reactive protein, IL6=interleukin 6, LDL-C=low density lipoprotein cholesterol, MI=myocardial infarction, NCEP=National Cholesterol Education Program, TC=total cholesterol, TG=triglycerides

Special Populations

Table 5. Special Populations[3-7,38-40]

Generic Name	Population and Precaution				
	Elderly/ Children	**Renal Dysfunction**	**Hepatic Dysfunction**	**Pregnancy Category**	**Excreted in Breast Milk**
Cholestyramine	No dosage adjustment required in the elderly. Safety and efficacy in children have not been established.*	No dosage adjustment required.	Not reported	C	No; use with caution.
Colesevelam	No dosage adjustment required in the elderly. Safety and efficacy in children <10 years of age for the treatment of heterozygous familial hyper-cholesterolemia have not been established. Safety and efficacy in children for adjunct treatment of type 2 diabetes have not been established.	No dosage adjustment required.	No dosage adjustment required.	B	No
Colestipol	No dosage adjustment required in the elderly. Safety and efficacy in children have not been established.	Not reported	Not reported	C	Unknown; use with caution.

*A usual pediatric dose of 240 mg/kg/day administered in two to three divided doses is recommended.

Adverse Drug Events

Table 6. Adverse Drug Events[3-7]

Adverse Event(s)	Cholestyramine	Colesevelam	Colestipol
Body as a Whole			
Accidental injury	-	4	-
Asthenia/weakness	-	4	✔
Back pain	-	3	✔
Fatigue	-	-	✔
Flu syndrome	-	3	-
Infection	-	10	-
Pain	-	5	-
Rash	✔	-	✔
Swelling of hands and feet	-	-	✔
Vitamin A deficiency	✔	-	-
Vitamin D deficiency	✔	-	-
Cardiovascular			
Angina	-	-	✔

Adverse Event(s)	Cholestyramine	Colesevelam	Colestipol
Chest pain	-	-	✔
Tachycardia	-	-	✔
Central Nervous System			
Dizziness/light-headedness	✔	-	✔
Headache	✔	6	✔
Insomnia	-	-	✔
Migraine	-	-	✔
Gastrointestinal			
Abdominal pain/discomfort	✔	5	✔
Anorexia	✔	-	✔
Constipation	✔	11	✔
Diarrhea	✔	5	✔
Dyspepsia	-	8	✔
Eructation	✔	-	-
Flatulence	✔	12	✔
Nausea	✔	4	✔
Steatorrhea	✔	-	-
Vomiting	✔	-	-
Hematological			
Hypoprothrombinemia associated with vitamin K deficiency	✔	-	-
Musculoskeletal			
Myalgia	-	2	✔
Osteoporosis	✔	-	-
Respiratory			
Cough increased	-	2	-
Pharyngitis	-	3	-
Rhinitis	-	3	-
Shortness of breath	-	-	✔
Sinusitis	-	2	-
Laboratory Test Abnormalities			
Abnormal liver function tests (alkaline phosphatase, alanine aminotransferase, aspartate aminotransferase)	✔	-	✔
Changes in triglyceride levels	✔	✔	✔

-Event not reported or incidence <1%.
✔ Percent not specified.

Contraindications/Precautions

Cholestyramine and colestipol are contraindicated in patients with hypersensitivity to bile acid sequestering resins or any component of the formulation or in bowel obstruction.[38,40] Cholestyramine is also contraindicated in complete biliary obstruction.[38] Colesevelam is contraindicated in a history of bowel obstruction, serum triglycerides >500 mg/dL and a history of hypertriglyceridemia-induced pancreatitis.[39]

Administration of bile acid sequestrants may produce or exacerbate constipation problems, and fecal impaction may develop. In addition, hemorrhoids may be worsened. Use of bile acid sequestrants is not recommended in patients with gastroparesis, other severe gastrointestinal motility disorders or a history of major gastrointestinal tract surgery. Patients with dysphagia or swallowing disorders should administer the oral suspensions of bile acid sequestrants.[38-40]

Administration of bile acid sequestrants with fat soluble vitamins and folic acid may interfere with absorption of these agents. In addition, caution should be exercised in patients susceptible of fat soluble vitamin deficiencies.[38-40]

Chronic administration of cholestyramine and colestipol, especially in high doses, may be associated with bleeding problems.[38,40]

Secondary causes of hyperlipidemia should be ruled out prior to therapy with cholestyramine. Caution should be exercised in the treatment of patients with serum triglycerides >300 mg/dL as therapy may cause increased concentrations. Therapy should be discontinued if triglyceride concentrations exceed 500 mg/dL or if hypertriglyceridemia-induced pancreatitis occurs.[38-40]

Colesevelam is not indicated for the management of type 1 diabetes, particularly in the acute management. It is also not indicated in type 2 diabetes as monotherapy and must be used as adjunct to diet, exercise and glycemic control with insulin or oral antidiabetic agents. Combination with dipeptidyl peptidase 4 inhibitors or thiazolidinediones has not been extensively evaluated.[39]

Questran Light® and some colesevelam- and colestipol-containing products contain phenylalanine.[38-40]

Drug Interactions

Table 7. Drug-Drug Interactions[41]

Drugs	Interaction	Mechanism
Bile acid sequestrants (cholestyramine, colestipol)	Corticosteroids	A decrease in the therapeutic effect of corticosteroids may occur.
Bile acid sequestrants (cholestyramine, colestipol)	Digoxin	A decrease in the bioavailability of digoxin may occur.
Bile acid sequestrants (cholestyramine, colestipol)	Loop diuretics	A decrease in the therapeutic effect of loop diuretics may occur.
Bile acid sequestrants (cholestyramine, colesevelam)	Thyroid hormones	A decrease in the therapeutic effect of thyroid hormones may occur.
Bile acid sequestrants (cholestyramine)	Anticoagulants	A decrease in the anticoagulant effect of anticoagulants may occur.
Bile acid sequestrants (cholestyramine)	Deferasirox	A decrease in the therapeutic effect of deferasirox may occur.
Bile acid sequestrants (cholestyramine)	Valproic acid	A decrease in the therapeutic effect of valproic acid may occur.

Dosage and Administration

Table 8. Dosing and Administration[3-7,38]

Generic Name	Adult Dose	Pediatric Dose	Availability
Cholestyramine	Adjunctive therapy to diet for the reduction of elevated serum cholesterol in patients with primary hypercholesterolemia who do not respond adequately to diet:* Powder: initial, 4 g Daily or BID; maintenance, 8 or 16 g/day administered in two divided doses†; maximum, 24 g/day (Prevalite®) Relief of pruritis associated with partial biliary obstruction:‡ Powder: initial, 4 g Daily or BID; maintenance, 8 or 16 g/day administered in two divided doses†; maximum, 24 g/day (Prevalite®)	Safety and efficacy in children have not been established.§	Powder: 4 gm

Generic Name	Adult Dose	Pediatric Dose	Availability
Colesevelam	Adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus: Powder: 3.75 g Daily Tablet: 3.75 g Daily or 1.875 g BID Adjunct to diet and exercise to reduce elevated LDL-C in adults with primary hyperlipidemia as monotherapy or in combination with a statin: Tablet: 3.75 g Daily or 1.875 g BID	Adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus: Safety and efficacy in children have not been established. Monotherapy or in combination with a statin to reduce LDL-C in boys and postmenarchal girls, 10 to 17 years of age, with heterozygous familial hyper-cholesterolemia:‖ Powder: 3.75 g Daily	Powder: 3.75 g Tablet: 625 mg
Colestipol	Adjunctive therapy to diet for the reduction of elevated serum total cholesterol and LDL-C in patients with primary hypercholesterolemia who do not respond adequately to diet:# Granules, powder: initial, 5 g (one packet or level teaspoon) Daily or BID; maintenance, increase dose by 5 g Daily or BID at one or two month intervals to a maintenance dose between 5 to 30 g/day administered Daily or in divided doses Tablet: initial, 2 g Daily or BID; maintenance, increase dose by 2 g Daily or BID at one or two month intervals to a maintenance dose between 2 to 16 g/day administered Daily or in divided doses	Safety and efficacy in children have not been established.	Granules: 5 g Powder: 5 g Tablet: 1 g

BID=twice-daily, LDL-C=low density lipoprotein cholesterol
*May be useful to lower low density lipoprotein cholesterol (LDL-C) in patients who also have hypertriglyceridemia, but it is not indicated where hypertriglyceridemia is the abnormality of most concern.
†Although the recommended dosing schedule is twice-daily, Prevalite® may be administered in 1 to 6 g doses per day.
‡Has been shown to have a variable effect on serum cholesterol in these patients. Patients with primary biliary cirrhosis may exhibit elevated cholesterol as part of their disease.
§A usual pediatric dose of 240 mg/kg/day administered in two to three divided doses is recommended.
‖If after an adequate trial of diet therapy the following findings are present: LDL-C remains ≥190 mg/dL or LDL-C remains ≥160 mg/dL and there is a positive family history of premature cardiovascular disease or two or more other cardiovascular disease risk factors are present in the pediatric patient.
#May be useful to lower LDL-C in patients who also have hypertriglyceridemia, but it is not indicated where hypertriglyceridemia is the abnormality of most concern.

Clinical Guidelines

Current guidelines are summarized in Table 9. The guidelines addressing the management of hypercholesterolemia are presented globally, addressing the role of various medication classes in the management of this disease.

As mentioned previously, colesevelam is Food and Drug Administration approved as adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes.[7] There is lack of strong recommendations within treatment guidelines on the use of bile acid sequestrants in the management of type 2 diabetes.[12,13] Although not a true recommendation, the Association of Clinical Endocrinologists/American College of Endocrinology notes that colesevelam reduces blood glucose levels in patients with type 2 diabetes, especially in patients not adequately controlled on metformin, a sulfonylurea or insulin.[12] The American Diabetes Association recommends that a hydroxymethylglutaryl coenzyme A reductase inhibitor (statin) be added to lifestyle therapy, regardless of baseline lipid levels, in patients with diabetes, and that combination therapy with other lipid lowering agents should be considered if lipid targets are not achieved.[13]

Table 9. Clinical Guidelines

Clinical Guideline	Recommendations
National Cholesterol Education Program: **Implications of Recent Clinical Trials for the National Cholesterol Education Program Adult Treatment Panel III Guidelines (2004)**[8]	• Therapeutic lifestyle changes (TLC) remain an essential modality in clinical management. • When low density lipoprotein cholesterol (LDL-C) lowering drug therapy is employed in high risk or moderately high risk patients, it is advised that intensity of therapy be sufficient to achieve ≥30 to 40% reduction in LDL-C levels. If drug therapy is a component of cholesterol management for a given patient, it is prudent to employ doses that will achieve at least a moderate risk reduction. • Standard hydroxymethylglutaryl-coenzyme A (HMG-CoA) reductase inhibitors (statin) doses are defined as those that lower LDL-C levels by 30 to 40%. The same effect may be achieved by combining lower doses of statins with other drugs or products (e.g., bile acid sequestrants, ezetimibe, nicotinic acid, plant stanols/sterols). • When LDL-C level is well above 130 mg/dL (e.g., ≥160 mg/dL), the dose of statin may have to be increased or a second agent (e.g., a bile acid sequestrant, ezetimibe, nicotinic acid) may be required. Alternatively, maximizing dietary therapy (including use of plant stanols/sterols) combined with standard statin doses may be sufficient to attain goals. • Fibrates may have an adjunctive role in the treatment of patients with high triglycerides (TG) and low high-density lipoprotein cholesterol (HDL-C), especially in combination with statins. • In high risk patients with high TG or low HDL-C levels, consideration can be given to combination therapy with fibrates or nicotinic acid and a LDL lowering agent. • Several clinical trials support the efficacy of nicotinic acid, which raises HDL-C, for reduction of coronary heart disease (CHD) risk, both when used alone and in combination with statins. The combination of a statin with nicotinic acid produces a marked reduction of LDL-C and a striking rise in HDL-C. <u>Treatment of heterozygous familial hypercholesterolemia</u> • Begin LDL-C lowering drugs in young adulthood. • TLC indicated for all persons. • Statins, first line of therapy (start dietary therapy simultaneously). • Bile acid sequestrants (if necessary in combination with statins). • If needed, consider triple drug therapy (statins and bile acid sequestrants and nicotinic acid). <u>Treatment of homozygous familial hypercholesterolemia</u> • Statins may be moderately effective in some persons. • LDL-pheresis currently employed therapy (in some persons, statin therapy may slow down rebound hypercholesterolemia).

Clinical Guideline	Recommendations
	Treatment of familial defective apolipoprotein B-100 • TLC indicated. • All LDL-C lowering drugs are effective. • Combined drug therapy required less often than in heterozygous familial hypercholesterolemia. Treatment of polygenic hypercholesterolemia • TLC indicated for all persons. • All LDL-C lowering drugs are effective. • If necessary to reach LDL-C goals, consider combined drug therapy.
National Cholesterol Education Program: **Third Report of the National Cholesterol Education Program Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) Final Report (2002)**[1]	General recommendations • With regards to TLC, higher dietary intakes of omega-3 fatty acids in the form of fatty fish or vegetable oils are an option for reducing risk for CHD. This recommendation is optional because the strength of evidence is only moderate at present. National Cholesterol Education Program supports the American Heart Association's recommendation that fish be included as part of a CHD risk reduction diet. Fish in general is low in saturated fat and may contain some cardioprotective omega-3 fatty acids. However, a dietary recommendation for a specific amount of omega-3 fatty acids is not made. • Initiate LDL lowering drug therapy with a statin, bile acid sequestrant or nicotinic acid. • Statins should be considered as first line drugs when LDL lowering drugs are indicated to achieve LDL-C treatment goals. • After six weeks if LDL-C goal is not achieved, intensify LDL lowering therapy. Consider a higher dose of a statin or add a bile acid sequestrant or nicotinic acid. Statins • Statins should be considered as first-line drugs when LDL-lowering drugs are indicated to achieve LDL treatment goals. Bile acid sequestrants • Bile acid sequestrants should be considered as LDL lowering therapy for patients with moderate elevations in LDL-C, for younger patients with elevated LDL-C, for women with elevated LDL-C who are considering pregnancy and for patients needing only modest reductions in LDL-C to achieve target goals. • Bile acid sequestrants should be considered in combination therapy with statins in patients with very high LDL-C levels. Nicotinic acid • Nicotinic acid should be considered as a therapeutic option for higher risk patients with atherogenic dyslipidemia. • Nicotinic acid should be considered as a single agent in higher risk patients with atherogenic dyslipidemia who do not have a substantial increase in LDL-C levels, and in combination therapy with other cholesterol lowering drugs in higher risk patients with atherogenic dyslipidemia combined with elevated LDL-C levels. • Nicotinic acid should be used with caution in patients with active liver disease, recent peptic ulcer, hyperuricemia, gout and type 2 diabetes. • High doses of nicotinic acid (>3 g/day) generally should be avoided in patients with type 2 diabetes, although lower doses may effectively

Clinical Guideline	Recommendations
	treat diabetic dyslipidemia without significantly worsening hyperglycemia. Fibric acid derivatives (fibrates) • Fibrates can be recommended for patients with very high TG to reduce risk for acute pancreatitis. • They also can be recommended for patients with dysbetalipoproteinemia (elevated beta-very LDL). • Fibrate therapy should be considered an option for treatment of patients with established CHD who have low levels of LDL-C and atherogenic dyslipidemia. • They also should be considered in combination with statin therapy in patients who have elevated LDL-C and atherogenic dyslipidemia. Omega-3 fatty acids • Omega-3 fatty acids (e.g., linolenic acid, docosahexaenoic acid [DHA], eicosapentaenoic acid [EPA]) have two potential uses. • In higher doses, DHA and EPA lower serum TGs by reducing hepatic secretion of TG-rich lipoproteins. They represent alternatives to fibrates or nicotinic acid for treatment of hypertriglyceridemia, particularly chylomicronemia. Doses of 3 to 12 g/day have been used depending on tolerance and severity of hypertriglyceridemia. • Recent trials also suggest that relatively high intakes of omega-3 fatty acids (1 to 2 g/day) in the form of fish, fish oils or high-linolenic acid oils will reduce the risk for major coronary events in persons with established CHD. Omega-3 fatty acids can be a therapeutic option in secondary prevention (based on moderate evidence). The omega-3 fatty acids can be derived from either foods (omega-3 rich vegetable oils or fatty fish) or from fish-oil supplements. More definitive trials are required before strongly recommending relatively high intakes of omega-3 fatty acids (1 to 2 g/day) for either primary or secondary prevention.
American Heart Association/American College of Cardiology/National Heart, Lung, and Blood Institute: **American Heart Association/American College of Cardiology Guidelines for Secondary Prevention for Patients With Coronary and Other Atherosclerotic Vascular Disease: 2006 Update (2006)**[42]	Lipid management • For patients without atherosclerotic disease, including those with other risk factors, recommendations of the National Cholesterol Education Program guidelines and their 2004 update should still be considered current. • Therapeutic options to reduce non-HDL-C include the following: more intense LDL-C lowering therapy, or niacin (after LDL-C lowering therapy) or fibrate therapy (after LDL-C lowering therapy). • If TGs are ≥500 mg/dL, therapeutic options to prevent pancreatitis are fibrate or niacin before LDL lowering therapy. Treat LDL-C to goal after TG lowering therapy. • Dietary supplement niacin must not be used as a substitute for prescription niacin. All patients with coronary and other atherosclerotic vascular disease • In addition to other lifestyle modifications, increased consumption of omega-3 fatty acids in the form of fish or in capsule form (1 g/day) for risk reduction is encouraged. For treatment of elevated TGs, higher doses are usually necessary for risk reduction.
Institute for Clinical Systems Improvement:	• Diet and exercise are the cornerstones of treatment for asymptomatic patients with dyslipidemia. TLC may include diet, aerobic exercise,

Clinical Guideline	Recommendations
Lipid Management in Adults (2009)[9]	weight management, smoking cessation, evaluation of alcohol consumption, sterol and stanol ester nutritional supplement and fish oil (EPA-DHA). • Omega-3 fats do not affect LDL levels but may help protect the heart in other ways. Trials have suggested that omega-3 fats reduce the risk of heart attack and death from heart disease for those who already have heart disease. • No primary prevention trials have addressed pharmacologic lipid treatment in persons at low risk for CHD. The incidence of CHD in men <40 years and premenopausal women is very low, and drug treatment in these groups is discouraged. • Primary prevention trials of pharmacologic lipid lowering have not shown a decrease in mortality, although most trials have shown a 30% reduction in CHD events. Trial populations have consisted mostly of middle-aged men, some with other risk factors. Similar benefit in higher-risk women can be assumed but has not been demonstrated. Monotherapy • Patients with risk factors for CHD but no history of disease who receive lipid lowering therapy are likely to experience a decreased risk of CHD. • Patients with a history of CHD often benefit from statin therapy and trials have consistently shown a decrease in risk of death from CHD. • Specific statin and dose should be selected based on cost and amount of lipid lowering required. • Based on the information above, for patients with established CHD or CHD risk equivalents, the use of a statin is recommended. • Statins are the drugs of choice for lowering LDL-C, and aggressive treatment should be pursued. Statins also have a modest effect on reducing TGs and increasing HDL-C. Several trials with clinical endpoints support the use of statins in primary and secondary prevention. • In patients receiving a statin who experience myalgias, it is recommended that a lower dose or another statin be tried. A 10 to 14 day vacation from a statin can also be considered as a diagnostic maneuver to see if myalgia symptoms abate. The evidence is inconclusive at this time for treating myalgia with Vitamin D and coenzyme Q. • If patients are intolerant to a statin, they should try the other statins in reduced doses before the medication class is deemed inappropriate. • If patients are unable to take a statin, bile acid sequestrants, niacin, fibric acid derivatives and ezetimibe are available. • The bile acid sequestrants reduce LDL-C, but they can increase TGs so should only be used as monotherapy in patients with a baseline TG ≤200 mg/dL. • Niacin has a greater effect on HDL-C than other currently available lipid medications. To improve tolerability and compliance, doses of niacin need to be titrated. • Fibric acid derivatives have a variable effect on LDL-C. Fenofibrate may be more effective at lowering LDL-C than gemfibrozil. They are usually reserved for hypertriglyceridemia or for an isolated low HDL-C. • Ezetimibe mainly reduces LDL-C, with minimal effect on TGs or HDL-C. No clinical outcome trials are currently available, but ezetimibe

Clinical Guideline	Recommendations
	appears useful for reducing LDL-C in patients who cannot take a statin and in combination with other LDL reducing medications. Combination therapy • Although combination therapy is not supported by outcome-based trials, some high risk patients will require combination therapy. These patients will most likely have CHD. • Using low doses of two complementary agents can often reduce LDL-C to a greater extent than a higher dose of either agent, with fewer side effects and possibly less cost. • In very resistant cases, triple therapy may be required. • Combination of a cholesterol lowering drug with a TG lowering drug to achieve the non-HDL-C goal may be most warranted in patients with established coronary artery disease who are a very high risk of recurrent coronary events. • Combining nicotinic acid with a statin is favorable for improving LDL-C, HDL-C and TGs. • Use of fibric acid derivatives leads to effective decreases in TGs and increased HDL-C, but the effect on LDL-C is varied. • An increased incidence of severe myopathy has been reported when a statin was combined with nicotinic acid or fibric acid derivatives. • In general, the combination of a statin and a fibric acid derivative raises the risk of myopathy and rhabdomyolysis. Aspirin • Dosage appears unimportant, usually ranging from 60 mg every other day up to 325 mg/day. • Secondary prevention trials have demonstrated reduced cardiovascular and cerebrovascular endpoints. • Primary prevention trials in patients not selected for cardiovascular risk factors have shown minimal benefit. • Patients with hyperlipidemia are at intermediate risk and may derive greater benefit from aspirin than the lower risk populations evaluated in primary prevention trials. The recommendation of aspirin in hyperlipidemic patients is supported by this reasoning, and by the low cost and risk of this therapy.
American Heart Association: **Drug Therapy of High Risk Lipid Abnormalities in Children and Adolescents: A Scientific Statement From the American Heart Association (2007)**[43]	• For children meeting criteria for lipid-lowering drug therapy, a statin is recommended as first line treatment. The choice of statin is dependent upon preference but should be initiated at the lowest dose once daily, usually at bedtime. • For patients with high risk lipid abnormalities, the presence of additional risk factors or high risk conditions may reduce the recommended LDL level for initiation of drug therapy and the desired target LDL levels. Therapy may also be considered for initiation in patients <10 years of age. • Additional research regarding drug therapy of high risk lipid abnormalities in children is needed to evaluate the long term efficacy and safety and impact on the atherosclerotic disease process. • Niacin is rarely used to treat the pediatric population. • Given the reported poor tolerance, the potential for very serious adverse effects, and the limited available data, niacin cannot be routinely recommended but may be considered for selected patients. • This guideline does not contain recommendations regarding the use of

Clinical Guideline	Recommendations
	omega-3 acid ethyl esters.
European Society of Cardiology and Other Societies: **Guidelines on Cardiovascular Disease Prevention in Clinical Practice (2007)**[10]	• Statins are first line drugs for lowering LDL-C. • Bile acid sequestrants can serve as effective lipid lowering alternatives. • Bile acid sequestrants tend to increase TG; therefore, should only be used when TG are <180 mg/dL or given in conjunction with TG lowering agents. • Niacin is considered an effective lipid lowering agent but flushing may limit use. • Niacin is more effective in increasing HDL-C than fibrates. • When TGs are 450 to 900 mg/dL, either fibrates or statins may be used as first line drugs, and niacin is considered a good drug for selected patients. • Fish oils are also TG lowering agents and might be useful as a third line therapy for patients with hypertriglyceridemia resistant to or intolerant of fibrates or niacin or in combination with other TG lowering drugs. • Combination therapy may be used in patients needing additional therapy to reach goals and the selection of appropriate drugs should vary based upon lipid levels.
American Association of the Study of Liver Disease: **Primary Biliary Cirrhosis (2009)**[11]	Therapy for primary biliary cirrhosis (PBC) • Ursodeoxycholic acid in a dose of 13 to 15 mg/kg/day orally is recommended for patients with PBC who have abnormal liver enzyme values regardless of histologic stage. • For patients requiring bile acid sequestrants, ursodeoxycholic acid should be given two to four hours before or after ingestion. • Bile acid sequestrants should be used as initial therapy for patients with PBC who have pruritis. • The following agents can be used for pruritis refractory to bile acid sequestrants: rifampicin, oral opiate antagonists (such as naltrexone) and sertraline. • Management of dry eyes can include the following: o Artificial tears as initial therapy. o Pilocarpine or cevimeline can be used in patients refractory to artificial tears. o Cyclosporine ophthalmic emulsion can be used in those refractory to other agents, preferably under the supervision of an ophthalmologist. • The following therapies should be reserved for xerostomia and dysphagia o Saliva substitutes can be tried. o Pilocarpine or cevimeline can be used if patients remain symptomatic despite saliva substitutes. o Moisturizers can be given for vaginal dryness.

Conclusions

The bile acid sequestrants are a class of medications whose major function is to decrease low density lipoprotein cholesterol (LDL-C) levels. In general, these agents work by binding to bile acids in the intestine through anion exchange causing an interruption of the reabsorption of bile acids. This reduction in bile acids leads to feedback regulation on the conversion of cholesterol to bile acids. Currently, three bile acid sequestrants are available: cholestyramine (Prevalite®, Questran®, Questran Light®), colesevelam (Welchol®) and colestipol (Colestid®, Flavored Colestid®). All agents are typically administered once or twice daily, and only cholestyramine and colestipol are available generically.

Colesevelam is more potent compared to either cholestyramine or colestipol, and colesevelam may be more easily administered and better tolerated compared to the other agents.[1,2]

The bile acid sequestrants are all Food and Drug Administration (FDA) approved for adjunct treatment in patients with hypercholesterolemia.[3-7] Cholestyramine is also FDA approved for relief of pruritis associated with partial biliary obstruction.[3,4] In addition, colesevelam is also FDA approved as monotherapy in children 10 to 17 years of age for the treatment of heterozygous familial hypercholesterolemia, and as adjunct therapy to diet and exercise to improve glycemic control in adults with type 2 diabetes.[7]

Clinical trial data consistently demonstrate the "superiority" of the bile acid sequestrants over placebo for the management of hyperlidpidemia.[16-25] In line with current clinical guidelines, results demonstrate that the addition of a bile acid sequestrant to another lipid lowering agent has the potential to produce further reductions in LDL-C levels compared to monotherapy with either of the agents.[20-27] In addition, treatment with cholestyramine has demonstrated mortality benefit in patients in reducing the risk of coronary heart disease death and/or nonfatal myocardial infarction.[28,29] Trials have also demonstrated as add on therapy to existing antidiabetic regiments, colesevelam achieves significant reductions in glycosylated hemoglobin compared to placebo.[30-37]

Therapeutic lifestyle changes, including diet, exercise and smoking cessation, remain an essential modality in the management of patients with hypercholesterolemia.[1,8,9] When LDL lowering is required, initial treatment with a hydroxymethylglutaryl coenzyme A reductase inhibitors (statins), a bile acid sequestrant or niacin is recommended; however, the statins are considered first line therapy for decreasing LDL-C levels.[1,8-10] If after six weeks of therapy lipid goals are not achieved on a statin alone, a dosage increase or the addition of a bile acid sequestrant or niacin should be considered.[1] Statins are also considered first line in the treatment of heterozygous familial hypercholesterolemia, but if required a bile acid sequestrant can be added to therapy.[8] The bile acid sequestrants are recognized as the therapy of choice for the management of pruritis associated with primary biliary cirrhosis.[11]

Appendix I: Utilization Within This Drug Class for DVHA: January 1, 2011 to June 30, 2011

Medication	Unique utilizers	# of Rx's	Market Share (%)	Plan Cost $	Avg $/Rx
Cholestyramine	45	65	46.10%	$5,520.08	$100.31
Micronized colestipol	22	32	22.70%	$4,243.35	$132.60
Welchol	9	17	12.06%	$5,056.34	$297.43
Cholestyramine light	15	15	10.64%	$953.78	$63.59
Prevalite	7	8	5.67%	$1,257.51	$157.19
Colestipol Hcl	4	4	2.84%	$415.00	$103.75
Class Total:	**102**	**141**	**100%**	**$18,446.06**	**$130.82**

Recommendations

In recognition of the established safety and efficacy of bile acid sequestrants, consensus clinical guideline recommendations, availability of generics and cost considerations, no changes are recommended to the current Department of Vermont Health Access (DVHA) approval criteria (below).

Questran®
- The patient has had a documented intolerance to cholestyramine powder.

Questran Light®
- The patient has had a documented intolerance to cholestyramine light powder.

Colestid®
- The patient has had a documented intolerance to colestipol tablets or granules.

Welchol®

- If being prescribed for lipid reduction, the patient has had a documented side effect, allergy, or treatment failure to cholestyramine and colestipol.

OR

- If being prescribed for additional improved glycemic control, the patient must have been unable to obtain a satisfactory hemoglobin A1C reduction with metformin and one other oral anti-diabetic agent.

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