

Role of Bile Acid Sequestrants in the Treatment of Type 2 Diabetes

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Type 2 diabetes is a complex disease that requires lifestyle modification and often pharmacological therapy. There are a variety of effective oral anti-diabetes agents to help control type 2 diabetes, thereby providing the opportunity for clinicians to select specific treatment(s) that meet the individual needs of a patient. This is particularly important for patients with type 2 diabetes, who often have comorbidities that can complicate the management and limit the pharmacological options for treatment. This review discusses the rationale for using a bile acid sequestrant (BAS) for the treatment of type 2 diabetes, the clinical effects of the only BAS approved for both glycemic and lipid control in the U.S. (colesevelam hydrochloride), and the appropriate place in type 2 diabetes therapy for a BAS.

CURRENT TREATMENTS FOR TYPE 2 DIABETES—Treatment strategies for type 2 diabetes evolve as new agents are approved, and evidence from clinical trials provides additional insight into the benefits and risks of existing treatments. The classes of oral antidiabetes agents include α -glucosidase inhibitors, biguanides, BASs, dipeptidyl peptidase-4 inhibitors, meglitinides, sulfonylureas, and thiazolidinediones (reviewed by Campbell [1]). This multitude of effective antidiabetes agents allows clinicians to individualize a treatment strategy to meet the needs of each patient. Although most antidiabetes agents are routinely used, each class is associated with specific safety concerns; for example, sulfonylureas have been associated with hypoglycemia, edema, and

weight gain (2–4), whereas thiazolidinediones have been associated with edema, congestive heart failure, and peripheral fractures (5,6). In addition, patients with type 2 diabetes often develop comorbidities as the disease progresses, including kidney disease, congestive heart failure, and coronary heart disease, which may be exacerbated by certain medications; for example, metformin should not be used in patients with renal insufficiency because of the risk of lactic acidosis (7), and thiazolidinediones are contraindicated in patients with advanced (New York Heart Association Class III and IV) congestive heart failure (5,6). Furthermore, newer agents, such as dipeptidyl peptidase-4 inhibitors, though seemingly safe, do not have an established long-term safety profile. Since its approval in 2006, sitagliptin has been implicated in the development of pancreatitis and serious allergic/hypersensitivity reactions (8). The BAS colesevelam, although only recently approved as an antidiabetes agent, has been used as a lipid-lowering agent for ~10 years (9).

BASs FOR THE TREATMENT OF TYPE 2 DIABETES—BASs were developed as lipid-lowering agents for the treatment of hypercholesterolemia. These agents, including cholestyramine, colesevelam, colestilan, colestimide, and colestipol, significantly reduce elevated LDL cholesterol levels and can be used as monotherapy or in combination with statins, fibrates, and/or cholesterol absorption inhibitors. The benefit of BAS therapy was demonstrated in the Lipid Research

Clinics Coronary Primary Prevention Trial, wherein cholestyramine reduced coronary heart disease, death, and nonfatal myocardial infarction by 19% compared with placebo in patients with hypercholesterolemia; the magnitude of the LDL and total cholesterol reductions was directly correlated to the reduced risk of coronary heart disease (10,11).

In addition to significant lipid-lowering properties, data from several studies suggest that BASs might also improve glycemic control in patients with type 2 diabetes (12–15). The initial observation of a glucose-lowering effect of a BAS was reported from a study that evaluated cholestyramine in patients with dyslipidemia and type 2 diabetes; 8 g cholestyramine twice daily reduced plasma glucose levels by 13% after 6 weeks (12). Subsequently, several small studies showed that colesevelam, colestilan, and colestimide each improved glycemic control in patients with type 2 diabetes (13–15). Colesevelam was evaluated in a large clinical trial program in adults with type 2 diabetes (16), wherein this agent was shown to significantly improve glycemic control (while also significantly reducing LDL cholesterol levels) when added to existing antidiabetes therapy in patients with type 2 diabetes (17–19). Although colestimide is approved in Japan, colesevelam is the only BAS approved in the U.S. for improving glycemic control in adults with type 2 diabetes.

MECHANISM(S) OF ACTION FOR THE GLYCEMIC EFFECT OF BASs

—The exact mechanism regulating the glycemic effect of a BAS remains unexplained; studies to elucidate the mechanism are ongoing. Potential mechanisms include effects on the farnesoid X receptor (the bile acid receptor) and TGR5 (a G protein–coupled receptor) within the intestine as well as effects on farnesoid X receptor within the liver, which may ultimately reduce endogenous glucose production (reviewed by Goldfine [20] and Staels [21]). Furthermore, BASs may affect secretion of incretin hormones, particularly glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide. In patients with type 2 diabetes and hypercholesterolemia, treatment with

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1,500 mg/day colestimide increased fasting GLP-1 levels (22). Similarly, treatment with 3.75 g/day colesevelam was shown to increase fasting GLP-1 levels as well as postprandial GLP-1 and glucose-dependent insulinotropic polypeptide levels (23). Additional studies are needed to fully elucidate the mechanism(s) for the beneficial glycemic effects of BASs.

CLINICAL TRIALS EVALUATING COLESEVELAM IN PATIENTS WITH TYPE 2 DIABETES

Efficacy

The combined glucose- and lipid-lowering effects of colesevelam were initially observed in a 16-week pilot study wherein adults with type 2 diabetes randomized to 3.75 g/day colesevelam experienced a significant reduction in HbA_{1c} (placebo-corrected change from baseline: -0.50%; $P = 0.007$), as well as a significant reduction in LDL cholesterol (-11.7%; $P = 0.007$) and LDL particle concentration (-15.5%; $P = 0.006$) (15,24). Subsequently, three randomized double-blind placebo-controlled studies examined the efficacy and safety of adding 3.75 g/day colesevelam to stable antidiabetes therapy (metformin- or sulfonylurea-based therapy [26 weeks] or insulin-based therapy [16 weeks]; summarized in Table 1) (16–19). In addition, patients who completed these double-blind studies were eligible to enroll in a 52-week open-label extension to further evaluate the safety and tolerability of colesevelam (25).

In all three double-blind studies with colesevelam, patients with inadequately controlled type 2 diabetes (HbA_{1c} 7.5–9.5%) despite ongoing antidiabetes therapy were recruited (16). In total, 1,064 patients were randomized (316 [metformin study] [17], 461 [sulfonylurea study] [18], and 287 [insulin study] [19]). Of the patients who completed the double-blind studies ($n = 760$) (17–19), 509 patients (67.0%) enrolled in the open-label extension, wherein all patients received 3.75 g/day colesevelam while continuing their background treatment with metformin, sulfonylurea, or insulin (alone or in combination with additional oral antidiabetes agents) (25).

The addition of colesevelam to existing antidiabetes therapy resulted in a significant reduction in HbA_{1c} in all three double-blind studies; placebo-corrected reductions in HbA_{1c} ranged from 0.50% (at 16 weeks on background insulin-based therapy; $P < 0.001$) (19) to 0.54% (at 26 weeks on either background metformin- or sulfonylurea-based therapy; $P < 0.001$ for both) (17,18). In addition, colesevelam reduced fasting plasma glucose (FPG) levels relative to placebo in all three studies (17–19). As a result of these beneficial glycemic effects, 47.7% of patients randomized to colesevelam (metformin study) (17), 47.5% in the sulfonylurea study (18), and 48.6% in the insulin study (19,26) achieved an HbA_{1c} reduction $\geq 0.7\%$ or an FPG reduction ≥ 30 mg/dL from baseline at study end.

In addition to a glycemic benefit, colesevelam resulted in a significant LDL cholesterol reduction in patients with type 2 diabetes; placebo-corrected LDL

cholesterol reductions ranged from 12.8% (at 16 weeks on background insulin-based therapy; $P < 0.001$) (19) to 15.9 and 16.7% (at 26 weeks on background metformin- or sulfonylurea-based therapy, respectively; $P < 0.001$ for both) (17,18). Post hoc analysis of data from the three double-blind studies was performed to determine the effect of colesevelam when added to patients with type 2 diabetes on existing statin therapy. In this population, the addition of colesevelam further reduced LDL cholesterol (placebo-corrected change from baseline: -15.6%; $P < 0.0001$) and HbA_{1c} (placebo-corrected change from baseline: -0.45%; $P < 0.0001$), despite existing statin therapy (27).

Overall, colesevelam improved the lipid profile of patients with type 2 diabetes in the three double-blind studies, since significant reductions in total cholesterol (placebo-corrected change from baseline: -7.2 and -5.0%) and non-HDL cholesterol (placebo-corrected change from baseline: -10.3 and -6.7%) occurred when colesevelam was added to metformin- or sulfonylurea-based therapy, respectively ($P < 0.001$ for all) (17,18). Reductions in total cholesterol and non-HDL cholesterol (placebo-corrected change from baseline: -3.7 and -4.0%, respectively) also occurred when colesevelam was added to insulin-based therapy, although these effects were not statistically significant (19). HDL cholesterol did not significantly change from baseline (17–19); however, triglyceride levels increased significantly when colesevelam was added to sulfonylurea- or insulin-based therapy

Table 1—Summary of the clinical effects of colesevelam in patients with type 2 diabetes

Study	<i>n</i>	Duration (weeks)	Background therapy	Treatment	Baseline HbA _{1c} (%)	Treatment difference: HbA _{1c} (%)	Treatment difference: LDL cholesterol (%)
Bays et al. (17)	316	26	Metformin-based therapy	Colesevelam 3.75 g/day ($n = 159$); Placebo ($n = 157$)	8.1	-0.54†	-15.9†
Fonseca et al. (18)	461	26	Sulfonylurea-based therapy	Colesevelam 3.75 g/day ($n = 230$); Placebo ($n = 231$)	8.2	-0.54†	-16.7†
Goldberg et al. (19)	287	16	Insulin-based therapy	Colesevelam 3.75 g/day ($n = 147$); Placebo ($n = 140$)	8.3	-0.50†	-12.8†
Goldfine et al. (25)	509	52	Metformin-, sulfonylurea-, or insulin-based therapy	Colesevelam 3.75 g/day ($n = 509$)	8.2	-0.3*	Not reported
Rigby et al. (42)	169	16	Metformin monotherapy	Colesevelam 3.75 g/day ($n = 57$); Rosiglitazone 4 mg/day ($n = 56$); Sitagliptin 100 mg/day ($n = 56$)	8.1	-0.3*‡¶	-11.6*‡

Treatment difference = colesevelam - placebo. *Mean change from baseline. † $P < 0.001$ vs. placebo. ‡ $P \leq 0.001$ vs. baseline. ¶ $P < 0.05$ vs. baseline.

(placebo-corrected change from baseline: 17.7 and 21.5%, respectively; $P < 0.001$ for both) (18,19). Because type 2 diabetes is a cardiovascular risk factor, aggressive management of the lipid profile is important to reduce overall cardiovascular risk. The lipid and apolipoprotein (apo) ratios indicative of cardiovascular risk were improved with colesevelam; the LDL cholesterol/HDL cholesterol and apoB/apoA-I ratios were significantly reduced with colesevelam in the three double-blind studies ($P < 0.01$ for all), suggesting an improvement in the overall lipid profile (17–19).

Safety and tolerability

In the double-blind studies, colesevelam was well tolerated in combination with various antidiabetes agents, including insulin (Table 2) (17–19). Rates of adverse events (AEs) were similar in both the colesevelam and placebo groups, and most AEs were unrelated to study treatment. The most common drug-related AEs with colesevelam were gastrointestinal in nature (mainly constipation) and often mild or moderate in severity (17–19). Gastrointestinal AEs are common with BAS treatment, since these agents bind to bile acids within the intestine.

Specific safety concerns for any pharmacological treatment used in patients with type 2 diabetes include risk of hypoglycemia and weight gain. Importantly, the incidence of hypoglycemia in the double-blind studies was similar with colesevelam and placebo. Weight management is an important component of type 2 diabetes therapy, and colesevelam was shown to be weight neutral; patients receiving colesevelam experienced a mean change in weight of -0.5 kg (metformin study) (17), -0.01 kg (sulfonyleurea study) (18), and 0.6 kg (insulin study) (19). Compliance with colesevelam was 92.7–93.3% in the double-blind studies (17–19) and 88.5% in completers of the 52-week open-label extension (25), suggesting colesevelam was well tolerated.

RATIONALE FOR USING BASs IN THE TYPE 2 DIABETES DISEASE CONTINUUM

Prediabetes/early type 2 diabetes

Glycemic control follows a continuum from normal glucose tolerance to impaired glucose tolerance/prediabetes to type 2 diabetes. Prediabetes is defined by the American Diabetes Association (ADA) and

the American Association of Clinical Endocrinologists (AACE)/American College of Endocrinology (ACE) as impaired fasting glucose (FPG 100–125 mg/dL) and/or impaired glucose tolerance (2-h post-stimulation [with 75 g glucose] 140–199 mg/dL) (28,29). Individuals with prediabetes are at an increased risk of developing type 2 diabetes (by 5- to 15-fold) (30) and are also at increased cardiovascular risk (31,32). Early control of hyperglycemia is important, since type 2 diabetes begins to develop 5–20 years before diagnosis, at which time there is marked insulin resistance, increased endogenous glucose production, and progressive β -cell failure (33). Identifying and managing prediabetes may have the potential to reduce the significant morbidity and mortality associated with type 2 diabetes by slowing or preventing its progression (29).

Colesevelam represents a novel treatment strategy for patients with prediabetes, improving both the lipid profile and glycemic control in this population (reviewed by Y.H. [34]). Post hoc analysis of data from a 24-week study showed that 3.75 g/day colesevelam reduced LDL cholesterol (placebo-corrected change from baseline: -13.2% ; $P < 0.001$) and FPG (placebo-corrected change from baseline: -4.0 mg/dL) in patients with hypercholesterolemia and prediabetes (35). A subsequent prospective clinical study evaluated the lipid- and glucose-lowering effects of colesevelam in patients with hypercholesterolemia and prediabetes (ClinicalTrials.gov identifier: NCT00570739) (36); in these patients, colesevelam significantly reduced LDL cholesterol (placebo-corrected change from baseline: -15.6% ; $P < 0.001$) and FPG levels (placebo-corrected change from baseline: -2.0 mg/dL; $P = 0.02$) (37).

A consensus statement from AACE/ACE recommends controlling both lipids (to reduce cardiovascular risk) and hyperglycemia (to reduce risk of progression to type 2 diabetes) in patients with prediabetes (30). Therefore, a BAS may be an appropriate treatment option based on its dual ability to reduce LDL cholesterol and glucose levels. No drug is currently approved to reduce hyperglycemia in patients with prediabetes; however, colesevelam may be used to further reduce LDL cholesterol in the appropriate patient with prediabetes, with the added benefit of an improvement in hyperglycemia. Additional research is needed to evaluate whether colesevelam prevents

or inhibits conversion from prediabetes to type 2 diabetes.

Early type 2 diabetes

The goal of antidiabetes therapy is to reduce HbA_{1c} to $<7.0\%$ (ADA recommendation) (28) or $\leq 6.5\%$ (AACE/ACE recommendation) (38,39). Furthermore, patients with recently diagnosed/early type 2 diabetes (and no comorbidities) should attain an HbA_{1c} as close to normal as possible ($<6.0\%$), while balancing against the risk of hypoglycemia (28,38,39). Both ADA and AACE/ACE recommend lifestyle modification in combination with antidiabetes monotherapy at the time of diagnosis (28,38,39), with persistent monitoring every 2–3 months until glycemic goals are achieved. Although ADA and AACE/ACE continue to support initiation of antidiabetes treatment with monotherapy, there has been a shift toward more intensive treatment, particularly immediately after diagnosis. Therapy intensification can include uptitration of oral antidiabetes monotherapy, initiation of oral antidiabetes agent combination therapy, and/or initiation of insulin therapy. Importantly, achieving glycemic control early in the type 2 diabetes continuum has been shown to preserve β -cell function (40) and confer lasting benefits in risk of vascular complications (41).

Metformin is the recommended first-line treatment for type 2 diabetes. However, metformin monotherapy often does not reduce HbA_{1c} adequately for patients to achieve glycemic control; therefore, additional therapies must be added. In the metformin study, the addition of 3.75 g/day colesevelam to ongoing metformin monotherapy significantly reduced HbA_{1c} (placebo-corrected change from baseline: -0.47% ; $P < 0.001$) (17), suggesting colesevelam may be beneficial early in the disease continuum to rapidly reduce glucose levels. In fact, 33 patients (22.3%) achieved HbA_{1c} $<7.0\%$ when colesevelam was added to their metformin-based therapy (17). A subsequent study evaluated the efficacy of adding 3.75 g/day colesevelam, 4 mg/day rosiglitazone, or 100 mg/day sitagliptin to metformin monotherapy (42). All three treatments significantly reduced HbA_{1c} compared with baseline (-0.3% [colesevelam], -0.6% [rosiglitazone], and -0.4% [sitagliptin]; $P < 0.05$ for all); however, colesevelam significantly reduced LDL cholesterol levels as well (-11.6% ; $P = 0.0012$), suggesting colesevelam may be an ideal second-line treatment option

Table 2—Summary of AEs associated with colesevelam in patients with type 2 diabetes

Study	n	Duration (weeks)	Background therapy	Treatment	AEs
Bays et al. (17)	316	26	Metformin-based therapy	Colesevelam 3.75 g/day (n = 159); placebo (n = 157)	<ul style="list-style-type: none"> Eight patients receiving colesevelam (four receiving placebo) withdrew because of AEs; of the AEs in the colesevelam group, six were considered drug-related. Constipation was the most common drug-related AE with colesevelam. No weight gain occurred with colesevelam. One patient reported (mild) hypoglycemia with colesevelam. Eighteen patients receiving colesevelam (nine receiving placebo) withdrew because of AEs. Constipation was the most common drug-related AE in both treatment groups. No weight gain occurred with colesevelam. Six patients receiving colesevelam (two receiving placebo) reported hypoglycemia. Five patients receiving colesevelam (two receiving placebo) withdrew because of AEs. Constipation, dyspepsia, hypoglycemia, flatulence, and nausea were the most common drug-related AEs with colesevelam. No weight gain occurred with colesevelam. Nine patients receiving colesevelam (eleven receiving placebo) reported hypoglycemia. Thirty-five patients receiving colesevelam withdrew because of AEs. Constipation and flatulence were the most common drug-related AEs. No weight gain occurred with colesevelam. Seventeen patients reported hypoglycemia (one episode of severe hypoglycemia). Three patients receiving colesevelam withdrew because of AEs. Eighteen patients receiving colesevelam reported drug-related AEs; the most common were gastrointestinal in nature. No weight gain occurred with colesevelam.
Fonseca et al. (18)	461	26	Sulfonylurea-based therapy	Colesevelam 3.75 g/day (n = 230); placebo (n = 231)	<ul style="list-style-type: none"> Eighteen patients receiving colesevelam (nine receiving placebo) withdrew because of AEs. Constipation was the most common drug-related AE in both treatment groups. No weight gain occurred with colesevelam. Six patients receiving colesevelam (two receiving placebo) reported hypoglycemia. Five patients receiving colesevelam (two receiving placebo) withdrew because of AEs. Constipation, dyspepsia, hypoglycemia, flatulence, and nausea were the most common drug-related AEs with colesevelam. No weight gain occurred with colesevelam. Nine patients receiving colesevelam (eleven receiving placebo) reported hypoglycemia. Thirty-five patients receiving colesevelam withdrew because of AEs. Constipation and flatulence were the most common drug-related AEs. No weight gain occurred with colesevelam. Seventeen patients reported hypoglycemia (one episode of severe hypoglycemia). Three patients receiving colesevelam withdrew because of AEs. Eighteen patients receiving colesevelam reported drug-related AEs; the most common were gastrointestinal in nature. No weight gain occurred with colesevelam.
Goldberg et al. (19,26)	287	16	Insulin-based therapy	Colesevelam 3.75 g/day (n = 147); placebo (n = 140)	<ul style="list-style-type: none"> Eighteen patients receiving colesevelam (nine receiving placebo) withdrew because of AEs. Constipation, dyspepsia, hypoglycemia, flatulence, and nausea were the most common drug-related AEs with colesevelam. No weight gain occurred with colesevelam. Nine patients receiving colesevelam (eleven receiving placebo) reported hypoglycemia. Thirty-five patients receiving colesevelam withdrew because of AEs. Constipation and flatulence were the most common drug-related AEs. No weight gain occurred with colesevelam. Seventeen patients reported hypoglycemia (one episode of severe hypoglycemia). Three patients receiving colesevelam withdrew because of AEs. Eighteen patients receiving colesevelam reported drug-related AEs; the most common were gastrointestinal in nature. No weight gain occurred with colesevelam.
Goldfine et al. (25)	509	52	Metformin-, sulfonylurea-, or insulin-based therapy	Colesevelam 3.75 g/day (n = 509)	<ul style="list-style-type: none"> Eighteen patients receiving colesevelam (nine receiving placebo) withdrew because of AEs. Constipation, dyspepsia, hypoglycemia, flatulence, and nausea were the most common drug-related AEs with colesevelam. No weight gain occurred with colesevelam. Nine patients receiving colesevelam (eleven receiving placebo) reported hypoglycemia. Thirty-five patients receiving colesevelam withdrew because of AEs. Constipation and flatulence were the most common drug-related AEs. No weight gain occurred with colesevelam. Seventeen patients reported hypoglycemia (one episode of severe hypoglycemia). Three patients receiving colesevelam withdrew because of AEs. Eighteen patients receiving colesevelam reported drug-related AEs; the most common were gastrointestinal in nature. No weight gain occurred with colesevelam.
Rigby et al. (42)	169	16	Metformin monotherapy	Colesevelam 3.75 g/day (n = 57); rosiglitazone 4 mg/day (n = 56); sitagliptin 100 mg/day (n = 56)	<ul style="list-style-type: none"> Eighteen patients receiving colesevelam (nine receiving placebo) withdrew because of AEs. Constipation, dyspepsia, hypoglycemia, flatulence, and nausea were the most common drug-related AEs with colesevelam. No weight gain occurred with colesevelam. Nine patients receiving colesevelam (eleven receiving placebo) reported hypoglycemia. Thirty-five patients receiving colesevelam withdrew because of AEs. Constipation and flatulence were the most common drug-related AEs. No weight gain occurred with colesevelam. Seventeen patients reported hypoglycemia (one episode of severe hypoglycemia). Three patients receiving colesevelam withdrew because of AEs. Eighteen patients receiving colesevelam reported drug-related AEs; the most common were gastrointestinal in nature. No weight gain occurred with colesevelam.

providing significant glucose- and lipid-lowering benefits in patients with type 2 diabetes (42). The most common AE with metformin is diarrhea, occurring in up to 53% of patients who received metformin monotherapy in a clinical study (7). This gastrointestinal effect may be related to altered absorption of bile salts within the intestine (43). It is possible that the addition of a BAS to metformin may help offset the increased incidence of diarrhea, while improving glycemic control and the lipid profile (36). A study was recently completed that evaluated first-line combination therapy with metformin and colesevelam in patients with recently diagnosed type 2 diabetes (ClinicalTrials.gov identifier: NCT00570739) (36). Initial therapy with metformin plus colesevelam significantly reduced HbA_{1c} and LDL cholesterol levels compared with metformin monotherapy (placebo-corrected change from baseline: -0.3 and -16.3%, respectively; $P < 0.01$ for both) (44). Similar to the effects observed in the metformin study, the addition of 3.75 g/day colesevelam to sulfonylurea monotherapy significantly reduced HbA_{1c} (placebo-corrected change from baseline: -0.59%; $P < 0.001$) (18), suggesting that a sulfonylurea plus colesevelam may also be a suitable treatment strategy (possibly for patients who cannot tolerate metformin).

The ADA and American College of Cardiology Foundation recommend management of lipid levels in patients with type 2 diabetes to reduce overall cardiovascular risk; lipid goals for patients with type 2 diabetes include LDL cholesterol <70 mg/dL, non-HDL cholesterol <100 mg/dL, and apoB <80 mg/dL (45). Importantly, many patients with type 2 diabetes would benefit from lipid-lowering therapy (45). In the three double-blind studies, colesevelam significantly reduced LDL cholesterol (by 12.8–16.7%; $P < 0.001$ for all), both when used alone or in combination with statin therapy (17–19,27). Furthermore, studies have shown that colesevelam significantly reduced total cholesterol, non-HDL cholesterol, apoB, and high-sensitivity C-reactive protein levels in patients with type 2 diabetes (17–19), demonstrating that this treatment may help reduce overall cardiovascular risk.

Ideally, colesevelam would be a component of early, aggressive treatment in patients with type 2 diabetes, helping to improve achievement of both glycemic and LDL cholesterol goals. As colesevelam has been shown to significantly improve

glycemic control when added to metformin- and sulfonylurea-based therapy (17,18), this antidiabetes therapy fits into various type 2 diabetes treatment strategies. Importantly, colesevelam was associated with a low incidence of hypoglycemia (similar to placebo) and has not been shown to cause weight gain in double-blind studies in adults with type 2 diabetes (17–19). Based on the available data, the 2009 AACE/ACE treatment algorithm for glycemic control recommended colesevelam in combination with metformin (for patients with HbA_{1c} of 6.5–7.5%) (39), and the 2009 Joslin Diabetes Center guidelines for the pharmacological management of type 2 diabetes listed colesevelam as a treatment option for patients with type 2 diabetes (46).

Established type 2 diabetes

Despite the proven advantages of intensive antidiabetes therapy early in the disease, aggressive therapy may not be beneficial for all patients (47–49). Management of type 2 diabetes later in the disease continuum is particularly difficult, posing many efficacy and safety concerns. Evidence from recent studies suggested that duration of type 2 diabetes, advanced age, history of complications (serious hypoglycemia), and severe comorbidities may affect treatment response; as such, patients meeting the above criteria may experience adverse effects in response to intensive antidiabetes therapy (50). Individualized therapy may be the ideal approach for patients with established disease. It is believed that hypoglycemia is a major cause of increased morbidity and mortality in patients with longstanding type 2 diabetes and comorbidities (47). Medications such as sulfonylureas and insulin (which can cause hypoglycemia) may be problematic in these patients and should be used cautiously and often with a limited dose. It is essential that clinicians carefully balance the benefits and risks of any treatment in patients with longstanding and/or advanced type 2 diabetes. Because cardiovascular risk is increased with type 2 diabetes, management of the lipid profile is essential. As such, the ADA and AACE/ACE suggest initiating combination therapy when lipid goals are not achieved with lifestyle modification and monotherapy with a lipid-lowering agent (28,38,39).

Many antidiabetes agents have reduced efficacy when added as a third- or fourth-line agent to existing treatment in

patients with type 2 diabetes. However, colesevelam has been shown to maintain its efficacy. Specifically, colesevelam as add-on therapy further reduced HbA_{1c} by ~0.5% in the three double-blind studies (17–19), suggesting this treatment provides an added glycemic benefit regardless of existing antidiabetes therapy and/or duration of disease. Insulin is often a component of antidiabetes therapy later in the disease, although it may be appropriate for certain patients early in treatment. Colesevelam, 3.75 g/day, significantly reduced HbA_{1c} and LDL cholesterol (placebo-corrected change from baseline: -0.50 and -12.8%, respectively; $P < 0.001$ for both) after 16 weeks when added to insulin-based therapy (insulin-only therapy or insulin plus oral antidiabetes therapy) (19). Importantly, there was a low incidence of hypoglycemia when colesevelam was used in combination with insulin therapy (19), indicating that colesevelam may be useful for improving glycemic and lipid control in adults on stable insulin therapy and/or late in the disease process.

Because colesevelam is not systemically absorbed, this agent is not contraindicated in patients with renal or hepatic impairment or heart failure. This finding is particularly important in patients with longstanding type 2 diabetes who may have renal insufficiency, liver damage, or chronic heart failure and may not be able to take various medications, such as metformin or thiazolidinediones (5–7). Based on its well-established use as a lipid-lowering agent and efficacy when combined with many antidiabetes and/or lipid-lowering therapies, colesevelam may be an appropriate agent for use throughout the type 2 diabetes continuum, including in high-risk patients (with prediabetes) as well as late in the disease. However, colesevelam has not been extensively studied in combination with thiazolidinediones. Because hypoglycemia is considered a major, if not the main, cause of increased morbidity and mortality in patients with longstanding type 2 diabetes and comorbidities, colesevelam, with its low risk of hypoglycemia, is an ideal choice for antidiabetes therapy.

CONCLUSIONS—Clinical studies have demonstrated that colesevelam provides significant glycemic and lipid benefits in adults with type 2 diabetes. Colesevelam may be beneficial for patients with prediabetes by providing both lipid and glycemic benefits in this high-risk

population. The addition of colesevelam to stable metformin-, sulfonyleurea-, or insulin-based regimens resulted in significant reductions in HbA_{1c} and LDL cholesterol. The dual glucose- and lipid-lowering effect of colesevelam makes it a beneficial drug to add to existing treatment, since it may help patients achieve both glycemic and lipid goals. Colesevelam was well tolerated when used throughout the type 2 diabetes continuum in combination with various antidiabetes treatments, had a low incidence of hypoglycemia, and was not associated with weight gain. Importantly, the data from the studies with colesevelam highlight its efficacy in a “real-world” setting, since colesevelam was added to existing treatment without washout of prior antidiabetes therapies. In conclusion, BASs represent a novel treatment option for patients with type 2 diabetes, unique in their ability to modulate multiple cardiovascular risk factors. BASs can be added to existing antidiabetes and lipid-lowering therapies throughout the lifecycle of type 2 diabetes, both early and late in the disease, to further manage hyperglycemia and hypercholesterolemia.

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