REVIEW ARTICLE

Drugs Aging 2012; 29 (5): e1-e12
1170-229X/12/0005-0001

Glucose and Low-Density Lipoprotein Cholesterol Lowering in Elderly Patients with Type 2 Diabetes

Focus on Combination Therapy with Colesevelam HCl

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Abstract

The prevalence of type 2 diabetes mellitus is high among the elderly population. Treatment of elderly patients with type 2 diabetes presents challenges because of co-morbidities and the potential increase in the risk of adverse effects. Hyperlipidaemia is also common in the elderly population. Glucose- and lipid-lowering treatment in elderly patients should be individualized on the basis of the patient's life expectancy, health status and cardiovascular risk factors, and evidence-based guideline recommendations. Because elderly patients often have impaired renal and hepatic function, careful considerations must be made when selecting appropriate glucose- and lipid-lowering therapy. There are a number of potential safety issues associated with various glucose- and lipid-lowering therapies that are relevant to elderly patients, including increased risk of heart failure exacerbations, weight loss, increased risk of hypoglycaemia, increased risk of myopathy, and contraindications of

some agents in patients with hepatic or renal impairment. The bile acid sequestrant colesevelam HCl is unique compared with other glucose- and lipid-lowering therapies because it is the only product approved by the US Food and Drug Administration, as an adjunct to diet and exercise, to lower both glucose and low-density lipoprotein cholesterol (LDL-C) in adults with type 2 diabetes and primary hyperlipidaemia, respectively. Furthermore, colesevelam has been shown to have similar glucose- and lipid-lowering efficacy in patients aged <65 years and those aged ≥65 years. Colesevelam was not associated with weight gain, was associated with a low incidence of hypoglycaemia, and can be safely combined with a broad range of glucose-lowering agents (metformin, sulfonylureas and insulin) and lipid-lowering statins. Currently, colesevelam is available in tablet form and as a powder for oral suspension formulation; the latter may be of benefit to elderly patients with swallowing difficulties. As colesevelam has both glucose- and lipid-lowering effects, its use may reduce the drug burden in elderly patients receiving multiple agents for glucose and lipid lowering. Colesevelam may be a valuable treatment option as an add-on to existing glucose- and/or lipid-lowering therapy to help improve haemoglobin A_{1c} and to lower LDL-C levels in elderly patients with type 2 diabetes and primary hyperlipidaemia.

1. Introduction

Diabetes mellitus is a chronic disease characterized by persistent hyperglycaemia, which is associated with increased morbidity and mortality.[1] Globally, the age-standardized prevalence of diabetes in adults aged 20–79 years has been estimated at 8.3% in 2011, and is projected to increase to 9.9% by 2030.[2] The majority of individuals with diabetes (90%) have type 2 diabetes mellitus,[3] a progressive disease characterized by pancreatic β-cell dysfunction and increased insulin resistance.[1] Epidemiological data on diabetes by age group are limited, but US data indicate that the prevalence of diabetes is high among the elderly. In the US, the prevalence of diabetes increased by 62% from 1994 to 2003 among individuals >65 years of age.[4] It was estimated that 10.9 million individuals (26.9%) aged ≥65 years within the US had diabetes in 2010.[5]

Hyperlipidaemia is a major risk factor for cardiovascular complications in patients with type 2 diabetes, regardless of age.[6,7] Hyperlipidaemia in patients with type 2 diabetes is associated with high atherogenic risk and is characterized by elevated triglyceride levels, low high-density lipoprotein cholesterol (HDL-C) levels, and a shift towards small, dense, low-density lipoprotein particles.[6,8-10] Although low-density lipoprotein cholesterol (LDL-C) levels in patients with diabetes are generally similar to those in the general population,[8] patients with diabetes can benefit from LDL-C reduction, even in the absence of elevated LDL-C levels.[11] In addition, data from the Framingham Heart Study indicate that hyperlipidaemia, obesity and cardiovascular disease often precede the development of type 2 diabetes in older patients.[12] The overall prevalence of hyperlipidaemia (defined as an LDL-C level above that recommended by the National Cholesterol Education Program [NCEP] Adult Treatment Panel III [ATP III] {i.e. <160 mg/dL for patients with 0–1 risk factor, <130 mg/dL for those with multiple risk factors, and <100 mg/dL for those with coronary heart disease and coronary heart disease risk equivalents[13]} or treatment with a lipid-lowering agent) has been reported to be as high as 60.3% in patients aged ≥65 years.[14]

Although many treatments exist for control of glucose and lipid levels in patients with type 2 diabetes, some are contraindicated in the presence of conditions that may be prevalent in the elderly. In addition, some treatments are associated with an increased risk of adverse effects in

the general population and, to a greater degree, in elderly patients. It is important to tailor treatment to the needs of individual patients with type 2 diabetes, especially those who are elderly, in order to improve outcomes.[15] The bile acid sequestrant colesevelam HCl is an established treatment for lowering LDL-C levels in adults with primary hyperlipidaemia, but is not considered first-line lipid-lowering therapy in adults with diabetes, since statins are recommended first.[1] Colesevelam is approved in the US for use in combination with a statin, and could be used in patients with diabetes who require LDL-C lowering beyond that achieved with a statin. Colesevelam is also approved in Canada, the EU, Iceland and Norway for the treatment of hypercholesterolaemia. In January 2008, colesevelam was also approved by the US Food and Drug Administration (FDA) for improving glycaemic control in adults with type 2 diabetes.[16] In this review, the challenges associated with controlling hyperglycaemia and hyperlipidaemia in elderly patients are discussed, with a focus on colesevelam in the context of targeting appropriate glycaemic and lipid-lowering goals in the elderly population. This non-systematic review of the treatment of elderly patients with type 2 diabetes is based on manual literature searches.

2. Managing Hyperglycaemia and Hyperlipidaemia in the Elderly

Treatment of diabetes (type 1 or type 2) is often suboptimal, particularly in those aged ≥65 years.[14,17] Data from the National Health and Nutrition Examination Survey from 1999 to 2004 indicate that 50.9% of elderly patients with diabetes (type 1 or type 2) are treated pharmacologically; however, only 50.4% of treated patients achieve glycaemic control (defined as haemoglobin A_{1c} [HbA_{1c}] <7.0%).[14] Recent clinical trials in the type 2 diabetes patient population have been unable to show reduced cardiovascular events with aggressive HbA_{1c} targets.[18] The low percentage of elderly patients who received pharmacological treatment may be due to a range of issues relating to perceived vulnerability, comorbidity, tolerability, polypharmacy, less aggressive glycaemic targets and psychosocial issues.[14,15,19] Similarly, only 64.9% of elderly patients who received treatment to manage their hyperlipidaemia achieved the NCEP ATP III-recommended target LDL-C level.[14]

2.1 Hyperglycaemia

The American Diabetes Association (ADA), the American Association of Clinical Endocrinologists (AACE) and the International Diabetes Federation (IDF) recommend HbA_{1c} targets of <7.0%, ≤6.5% and <6.5%, respectively, in all non-pregnant adults with diabetes, although the ADA recommends that the goals be individualized on the basis of a number of factors, including age/life expectancy.[1,20,21] Less intensive glycaemic targets (e.g. HbA_{1c} <8.0%) are recommended in older adults with limited life expectancy, advanced diabetes complications and/or cardiovascular disease.[18,22] Alternatively, a significant minority of elderly patients with longer life expectancy might benefit from intensive management of hyperglycaemia with a target HbA_{1c} of <7.0%.[1,18,23] A study evaluating the implementation of American Geriatrics Society guidelines recommending an HbA_{1c} target of <8.0% in frail older adults (aged ≥55 years) found that patients had fewer hyperglycaemic episodes, lower HbA_{1c} values and greater use of glucose-lowering agents, but also found that there was a significant increase in the incidence of severe hypoglycaemia during the early implementation period.[24]

2.2 Hyperlipidaemia

Although primary hyperlipidaemia has specific typical characteristics, studies suggest that the benefit derived from lipid-lowering therapy with an HMG-CoA reductase inhibitor (statin) in terms of cardiovascular outcomes is comparable in patients with and without diabetes (type 1 or type 2).[8] The HPS (Heart Protection Study) and the CARDS (Collaborative Atorvastatin Diabetes Study) demonstrated that treatment with simvastatin or atorvastatin, respectively, significantly reduced the risk of cardiovascular events in patients with diabetes (type 1 or type 2 in the HPS and type 2 in the CARDS).[25,26] Furthermore, results

Table I. The American Diabetes Association (ADA), the National Cholesterol Education Program (NCEP), the American Association of Clinical Endocrinologists (AACE) and the International Diabetes Federation (IDF) lipid targets in patients with type 2 diabetes mellitus, and the ADA/American College of Cardiology Foundation (ACCF) lipid and lipoprotein targets in patients at cardiometabolic risk[1,20,21,28,29]

Guideline	Lipid and lipoprotein targets (mg/dL)				
	LDL-C	HDL-C	Non–HDL-C	TG	ApoB
Targets for patients with type 2 diabetes					
ADA	<70 (+CVD), <100 (–CVD)	>40 (male), >50 (female)	–	<150	–
NCEP	<70 (+CVD), <100 (–CVD)	–	<100[a] (+CVD), <130[a] (–CVD)	–	–
AACE	<70 (+CVD), <100 (–CVD)	>40 (male), >50 (female)	<100 (+CVD), <130 (–CVD)	<150	<80 (+CVD), <90 (–CVD)
IDF	<95	>39	–	<200	–
Targets for patients at cardiometabolic risk					
ADA/ACCF	<70 (highest-risk)[b], <100 (high-risk)[c]	–	<100 (highest-risk)[b], <130 (high-risk)[c]	–	<80 (highest-risk)[b], <90 (high-risk)[c]

a Target as a secondary goal when TG levels are ≥200 mg/dL; goal is 30 mg/dL higher than LDL-C goal.

b Patients with known CVD or diabetes with at least one additional CVD risk factor.

c Patients with diabetes but no other CVD risk factors, or without diabetes or CVD but with at least two additional CVD risk factors.

ApoB = apolipoprotein B; **CVD** = cardiovascular disease; **HDL-C** = high-density lipoprotein cholesterol; **LDL-C** = low-density lipoprotein cholesterol; **TG** = triglyceride(s); – indicates no target specified.

from the HPS indicated that the reduction in risk of cardiovascular events reported with statin therapy was similar in patients with and without diabetes (type 1 or type 2).[25] A meta-analysis of clinical studies evaluating statin therapy showed that patients with diabetes who were aged ≤65 and >65 years benefited to a similar extent from LDL-C lowering regardless of baseline lipid profile.[27]

Lipid-lowering targets for patients with type 2 diabetes or at cardiometabolic risk are shown in table I.[1,20,21,28] Slight variation exists among targets advocated by the ADA, NCEP, AACE and IDF for patients with type 2 diabetes,[1,20,21] and those recommended by the ADA/American College of Cardiology Foundation (ACCF) for patients at cardiometabolic risk.[28] Treatment guidelines often do not provide separate recommendations for elderly patients; however, treatment in elderly patients should be individualized on the basis of physiological/functional age.[30] The ADA recommends statin treatment in all patients with diabetes who have established cardiovascular disease, or those without cardiovascular disease and at least one cardiovascular risk factor who are >40 years of age, irrespective of baseline lipid values.[1]

Although the association between hyperlipidaemia and cardiovascular risk weakens with age, older patients have a higher baseline risk because of other risk factors, and may benefit more from lipid-lowering treatment.[31] Therefore, those expected to survive >1 year should be strongly considered for primary and secondary prevention efforts as recommended by the NCEP and ADA.[1,13]

3. Safety/Adherence Concerns in Elderly Patients with Type 2 Diabetes

The risk of hypoglycaemia with glucose-lowering agents is higher in elderly patients with type 2 diabetes because of altered pharmacokinetics, impaired metabolism, co-morbid conditions that can mask hypoglycaemia, impaired perception or isolation preventing early identification and treatment of hypoglycaemia, poor nutrition, polypharmacy, and/or cognitive impairment leading to non-adherence (e.g. reduced dose interval or increased dose taken in error).[19,32]

Reduced renal and hepatic function can be present in elderly patients,[33] and therefore, pharmacological agents must be selected carefully on the basis of where they are metabolized or

excreted from the body. Decreased renal function slows the drug metabolized through the kidneys, which can decrease drug clearance, resulting in increased plasma concentrations, which can potentially lead to adverse effects.[19] Consequently, doses of pharmacological agents may need to be adjusted in elderly patients. Congestive heart failure (CHF) is most common in the elderly, and diabetes is an independent predictor for CHF in the elderly.[34-36] In addition, elderly patients with type 2 diabetes often have other co-morbid conditions, including hypertension, coronary artery disease and hyperlipidaemia. The use of polypharmacy may lead to drug–drug interactions, altered drug pharmacokinetics and adherence issues.[19] Furthermore, difficulty swallowing, frailty and reduced manual dexterity may make some drugs more difficult to take.

4. Agents Used for the Treatment of Type 2 Diabetes in the Elderly

4.1 Agents Used for Managing Hyperglycaemia

Current treatment options for glucose control in type 2 diabetes are shown in table II. Oral glucose-lowering agents are widely used for the treatment of type 2 diabetes to control blood glucose levels. These agents include insulin secretagogues, including sulfonylureas (glipizide, glyburide and glimepiride) and meglitinides (repaglinide and nateglinide); biguanides (metformin); thiazolidinediones (rosiglitazone and pioglitazone); α-glucosidase inhibitors (acarbose); dipeptidyl peptidase-IV (DPP-IV) inhibitors (linagliptin, saxagliptin and sitagliptin); and bile acid sequestrants (colesevelam). Injectable glucose-lowering

Table II. Summary of classes of glucose-lowering agents used in type 2 diabetes mellitus[19,23,37-42]

Drug	Route	Site of action	Expected HbA_{1c} reduction (%)	Benefits relevant to elderly patients	AEs/precautions relevant to elderly patients
Insulin secretagogues					
Sulfonylureas	Oral	Pancreas	~1–2	Effective as monotherapy; AEs rare	Risk of hypoglycaemia higher in elderly
Meglitinides	Oral	Pancreas	~0.5–1.5	Can be used in patients with renal impairment	Risk of hypoglycaemia higher in elderly
Biguanides	Oral	Liver (and muscle, adipose tissue)	~1–2	Minimal risk of hypoglycaemia	Gastrointestinal AEs, weight loss; contraindicated in renal disease/dysfunction
Thiazolidinediones	Oral	Muscle, adipose tissue, possibly pancreas	~1–1.5	Minimal risk of hypoglycaemia	Cause bone loss and fractures, especially in older women; increase risk of myocardial infarction and may cause or worsen congestive heart failure
α-glucosidase inhibitors	Oral	Intestine	~0.5–1.0	Minimal risk of hypoglycaemia	Gastrointestinal AEs
Incretin-based therapies					
Dipeptidyl peptidase-IV inhibitors	Oral	Pancreas, intestine	~0.5–0.8	Minimal risk of hypoglycaemia	Dose adjustment required for renal impairment
Glucagon-like peptide-1 analogues	SC	Pancreas, intestine	~0.5–1.0	Aid in weight loss for patients who cannot exercise	Weight loss could be detrimental to frail, underweight patients
Insulin	SC	Liver, adipose tissue, muscle	No limit (theoretically)	Effective; therapy can be adjusted to prevent elevated blood glucose levels	High risk of hypoglycaemia; use and administration may be complex in elderly
Bile acid sequestrants	Oral	Liver, intestine, pancreas	0.4–0.9	Low incidence of AEs; available in powder formulation	Gastrointestinal AEs (constipation)

AEs = adverse events; **HbA_{1c}** = haemoglobin A_{1c}; **SC** = subcutaneous.

agents include glucagon-like peptide-1 (GLP-1) analogues (exenatide and liraglutide) and insulin (short and long acting). Traditionally, insulin is initiated when elevated blood glucose levels persist despite oral glucose-lowering therapy (generally starting with basal insulin and then transitioning to bolus insulin with meals) or when a patient presents with HbA_{1c} >9.0% and symptomatic hyperglycaemia, regardless of whether they are on treatment or are treatment-naive.[20]

4.1.1 Limitations of Glucose-Lowering Agents Used in the Treatment of Elderly Patients with Type 2 Diabetes

There are a number of potential safety issues associated with the use of various glucose-lowering agents that are relevant to elderly patients, which are summarized in table II.[19,23,37-39]

Chronic use of thiazolidinediones may cause bone loss, which can increase the risk of fractures, especially in older women.[43-45] Both thiazolidinediones and meglitinides can be used in patients with impaired renal function since these agents are not metabolized via the kidney; however, both classes of glucose-lowering agents require monitoring of liver function, and should be used with caution in patients with hepatic impairment.[19] Rosiglitazone may increase the risk of myocardial infarction.[46] In addition, thiazolidinediones can cause or exacerbate CHF in some patients; thus, monitoring for heart failure is required after initiating these drugs, and they are contraindicated in patients with established New York Heart Association functional class III or IV heart failure.[40,46,47] Based on the potential for rosiglitazone to increase cardiovascular risk, the marketing authorization for rosiglitazone-based medications in the EU has been suspended,[48] and, in the US, the FDA has created a Risk Evaluation and Mitigation Strategy (REMS) programme to restrict access and distribution and monitor patients taking the medication.[49] Recently, the FDA warned that use of pioglitazone for >1 year may be associated with an increased risk of bladder cancer, and therefore it should not be used in patients with active bladder cancer and should be used with caution in those with a history of bladder cancer.[50]

Metformin is contraindicated in patients with renal disease or dysfunction (serum creatinine levels of ≥1.5 mg/dL in males or ≥1.4 mg/dL in females),[41] and may not be suitable in elderly patients who are underweight or frail, those with hepatic impairment or those with CHF.[37,51] Recent recommendations on the use of metformin in patients with compromised renal function has suggested their safe use down to an estimated glomerular filtration rate of 30 mL/min/1.73 m^2.[52] Gastrointestinal effects may occur with metformin (metallic taste, anorexia, nausea, abdominal pain and diarrhoea), acarbose (abdominal discomfort, increased formation of intestinal gas and diarrhoea) and colesevelam (primarily constipation).[53] The gastrointestinal issues associated with metformin can be minimized by a slow initial titration as suggested by the ADA.[42]

The risk of hypoglycaemia with sulfonylureas and meglitinides is increased in the elderly, particularly in patients with renal impairment.[37] Although data are limited regarding the use of DPP-IV inhibitors in the elderly, DPP-IV inhibitors appear to have benign tolerability profiles and a low risk of hypoglycaemia; however, for those agents that are renally excreted, dose adjustments are necessary in patients with renal impairment.[37,54]

In the general adult diabetes population, α-glucosidase inhibitor use is uncommon, and this holds true in the elderly population, possibly as a result of its minimal effectiveness compared with other available glucose-lowering agents. In addition, α-glucosidase inhibitors are associated with gastrointestinal effects (flatulence and diarrhoea), should be avoided in patients with renal impairment, and may increase the risk of hypoglycaemia when combined with prandial insulin.[37]

Insulin use is complex and has a high risk of hypoglycaemia if taken inappropriately; therefore, if glycaemic control is achievable without it, insulin use should be avoided in elderly patients who have reduced cognitive function or poor manual dexterity.[37]

Some glucose-lowering agents affect weight. Sulfonylureas and thiazolidinediones are both associated with weight gain.[55] The DPP-IV inhibitors are generally weight neutral, but the GLP-1

analogues are associated with significant weight loss,[56,57] which, although useful in overweight or obese elderly patients, might potentially be less beneficial in frail elderly patients or patients with a low body mass index at baseline.

4.2 Agents Used for Managing Primary Hyperlipidaemia

Pharmacotherapy for the treatment of primary hyperlipidaemia across various co-morbidities focuses on statin therapy as first-line treatment, but allows for the addition of other lipid-lowering therapies depending on patient cholesterol values and co-morbidities, and avoidance of drug–drug interactions. Current treatment options for managing the lipid profile in adults with type 2 diabetes are summarized in table III. These options include statins, niacin, fibrates (gemfibrozil and fenofibrate), bile acid sequestrants (colesevelam, cholestyramine and colestipol), and cholesterol absorption inhibitors (ezetimibe). Statins are the first-line treatment for LDL-C lowering for all patients, including those with type 2 diabetes; however, their use may be restricted or contraindicated in some patients (e.g. because of drug–drug interactions).[1,8]

4.2.1 Limitations of Lipid-Lowering Agents Used in the Treatment of Elderly Patients with Type 2 Diabetes

The limitations of lipid-lowering agents in elderly patients with type 2 diabetes are summarized in table III.[30,38,58,59] Primary and secondary prevention trials have demonstrated the efficacy and tolerability of lipid-lowering therapy in elderly patients with hyperlipidaemia[60,61] and in patients with type 2 diabetes,[6,10] but data in elderly patients with type 2 diabetes are limited.

There are a number of potential safety issues associated with lipid-lowering therapy that are relevant to elderly patients with type 2 diabetes. In general, statins are well tolerated.[62,63] However, statin therapy has been associated with muscle injury and hepatotoxicity. According to information in the product labelling from controlled studies, 1–5% of patients receiving statins may develop

Table III. Summary of classes of lipid-lowering agents used in type 2 diabetes mellitus[30,38,58,59]

Drug	Route	Site of action	Effects on lipid profile	Benefits in elderly patients	AEs/precautions in elderly patients
HMG-CoA reductase inhibitors (statin)	Oral	Liver	↓LDL-C by 17–61% ↓TC by 11–48% ↓TG by 2–45% ↑ HDL-C by 2–16%	Low incidence of AEs	Increased risk of myopathy
Niacin	Oral	Adipose tissue, liver	↓LDL-C by 10–25% ↓TC by 10–25% ↓TG by 20–50% ↑HDL-C by 10–35%	Available in once-daily extended-release formulation	Can decrease glycaemic control
Fibrates	Oral	Liver	↓LDL-C by 5–20% ↓TC by 10–20% ↓TG by 20–55% ↑HDL-C by 1–34%	Low incidence of AEs	Contraindicated in patients with hepatic or severe renal impairment
Bile acid sequestrants	Oral	Intestine	↓LDL-C by 10–30% ↓TC by 10–25% ↑TG by up to 23% ↑HDL-C by 2–5%	Low incidence of AEs; available in powder formulation	Gastrointestinal AEs (constipation)
Cholesterol absorption inhibitors	Oral	Intestine	↓LDL-C by 15–18% ↓TC by 12–17% ↓TG by 7–14% ↑HDL-C by 1–5%	Low incidence of AEs	Use should be avoided in patients with hepatic impairment

AEs = adverse events; **HDL-C** = high-density lipoprotein cholesterol; **LDL-C** = low-density lipoprotein cholesterol; **TC** = total cholesterol; **TG** = triglycerides; ↑ = increases; ↓ = decreases.

myalgia, although the incidence of this is not significantly different to that in patients given placebo.[62] A review of a drug safety database, Qscan-FDA (DrugLogic, Inc., Reston, VA, USA), from January 1990 through to March 2002 identified 3339 cases of statin-associated rhabdomyolysis.[62] A subsequent analysis of data from November 1997 to March 2000 identified 612 cases of rhabdomyolysis, with one-half of the reported cases occurring in patients aged 51–75 years.[62] Concomitant use of gemfibrozil and niacin were found to increase the risk of statin-associated myopathy (primarily associated with statins that have a drug–drug interaction with gemfibrozil, including lovastatin, simvastatin and rosuvastatin).[62,64] In June 2011, the FDA initiated label changes for products containing simvastatin to include restrictions on the use of a simvastatin dose of 80 mg/day, because of an elevated risk of myopathy at this dosage.[65] The FDA recommends that simvastatin 80 mg/day should only be used in patients who have already taken this dose for ≥12 months without evidence of myopathy. Combination therapy may be a safer alternative to help patients achieve LDL-C goals without requiring high statin dosages such as these. Elevated liver enzyme levels during statin treatment are not uncommon, but studies have suggested that the incidence of aminotransferase levels of >3 times the upper limit of normal is approximately 1–3%, and is not significantly different to that in patients given placebo.[66-70] The FDA recently updated statin labels to recommend performing liver enzyme tests before initiation of therapy and as clinically indicated thereafter (as opposed to routine periodic monitoring as was previously recommended).[71] Importantly, there does not appear to be an association between increased age and risk of significant liver injury.[63] The updated statin labels also include a warning regarding reports of cognitive impairment associated with statin use, which may be of particular concern in elderly patients.[71]

Niacin has the potential to worsen glycaemic control,[59] although studies have shown that immediate-release niacin, as well as low doses of extended-release niacin, can be used safely in patients with type 2 diabetes.[72-74] There are also data suggesting that some statins may worsen glycaemic control or increase the risk of new-onset type 2 diabetes, as illustrated by findings with atorvastatin.[75-77] Bile acid sequestrants (colesevelam, cholestyramine and colestipol) are associated with gastrointestinal effects, primarily constipation.[78] Finally, the use of fibrates may be limited in some elderly patients because they are contraindicated in patients with hepatic or severe renal impairment.[79,80]

4.3 Role of Colesevelam in Managing Lipid and Glucose Levels

Bile acid sequestrants were initially approved for reducing LDL-C levels. However, cholestyramine and colesevelam have also been shown to exert significant glucose-lowering effects in patients with type 2 diabetes.[81-85] In 2008, colesevelam received approval from the FDA for improving glycaemic control in adults with type 2 diabetes.[16] In addition to a tablet formulation, colesevelam may be taken as an oral suspension, which may be beneficial for elderly patients who may have swallowing difficulties, and could facilitate patient adherence to treatment.

4.3.1 Efficacy

In three randomized, double-blind, placebo-controlled studies, colesevelam significantly lowered mean HbA_{1c} (treatment difference vs placebo: –0.50% to –0.54%; $p < 0.001$ for all) and LDL-C levels (–12.8% to –16.7%; $p < 0.001$ for all) in adults with type 2 diabetes when added to stable metformin-, insulin- or sulfonylurea-based therapy.[83-85] A *post hoc* analysis on pooled data from the three above-mentioned double-blind, placebo-controlled studies ($n = 1018$) showed that colesevelam significantly reduced the levels of mean HbA_{1c}, LDL-C, non–HDL-C and total cholesterol compared with placebo in both the <65 and ≥65 years of age subpopulations.[86,87] The effect of colesevelam on cardiovascular morbidity and mortality has not been established.

In addition, colesevelam has shown a dose-sparing effect on statin therapy when used in combination, but a statin dose potent enough to achieve a 30–40% reduction in LDL-C levels should be

targeted.[88-90] Therefore, combining colesevelam with a moderate dose of a statin may be appropriate for adults who have not achieved lipid targets with higher statin doses, or for adults who may be susceptible to adverse effects when receiving a high dose of a statin.[59] However, adults who require substantial LDL-C lowering may still need to receive a high-potency statin dose, either alone or in combination with additional LDL-C-lowering agents.

4.3.2 Safety and Tolerability

Colesevelam is not systemically absorbed; therefore, the potential for systemic adverse events is low, and patients receiving colesevelam do not require routine monitoring of liver function. In clinical studies, the overall incidence of adverse events with colesevelam was similar to placebo.[83-85] Colesevelam has also been shown to be weight neutral and have a low risk of hypoglycaemia.[83-85] The most common adverse event reported with colesevelam is constipation; clinical studies have shown that the incidence of constipation was higher with colesevelam compared with placebo.[83-85] Constipation could be more problematic for the elderly than for the general population.[91]

However, colesevelam increased triglyceride levels compared with placebo treatment ($p < 0.001$ when added to insulin- or sulfonylurea-based therapy).[83-85] Similarly, in the age-based subgroup analysis, triglyceride levels were significantly increased with colesevelam treatment in both age subgroups (colesevelam vs placebo treatment difference: <65 years, +14.7% [$p < 0.0001$]; ≥65 years, +14.2% [$p = 0.0036$]).[87] A number of studies have suggested an association between triglyceride levels and cardiovascular risk; however, this is controversial, with the effect size typically modest compared with other cardiovascular risk factors (including other lipid parameters).[92] In addition, although triglyceride levels are closely associated with type 2 diabetes, studies evaluating the association between triglycerides and cardiovascular risk often do not include type 2 diabetes as a confounding factor.[92] Because colesevelam increases triglyceride levels, it is contraindicated in patients with triglyceride levels of >500 mg/dL.[16]

5. Conclusions

The prevalence of type 2 diabetes is increasing among elderly individuals in the US and worldwide. Elderly patients with type 2 diabetes can be difficult to treat because of co-morbidities and an increased risk of adverse effects with pharmacological treatments. In addition, hyperlipidaemia represents a particular health concern among elderly patients with diabetes. The proven efficacy, once- or twice-daily dosing, and dual formulations of the bile acid sequestrant colesevelam make it a treatment option as an add-on to existing glucose-lowering therapy or lipid-lowering statins for control of primary hyperlipidaemia and hyperglycaemia in elderly patients with type 2 diabetes not achieving treatment targets. However, the effect of colesevelam on cardiovascular morbidity and mortality has not been established.

Acknowledgements

The editorial assistance provided by Mary Hines, Anna Mett and Lucy Whitehouse of *in*Science Communications was funded by Daiichi Sankyo, Inc. Joel C. Marrs declares no potential conflicts of interest, and did not receive funding for writing this manuscript.

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