

CASE STUDIES COMPENDIUM

Featuring:

Management Decisions in an Adult Comorbid Patient With Type 2 Diabetes Having Primary Hyperlipidemia

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Colesevelam Hydrochloride for Management of a Patient With Type 2 Diabetes Mellitus and Hyperlipidemia

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Faculty Disclosure

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Management Decisions in an Adult Comorbid Patient With Type 2 Diabetes Having Primary Hyperlipidemia

Key Point: Type 2 diabetes mellitus (T2DM) and primary hyperlipidemia are risk factors for cardiovascular disease (CVD) that warrant timely management of both disorders. An option for treating T2DM and primary hyperlipidemia is Welchol® (colesevelam HCl)*, which represents an effective and safe way to treat patients with elevated glycosylated hemoglobin (A1C) and low-density lipoprotein cholesterol (LDL-C).

Nancy† is a 60-year-old Caucasian woman who works in a corporate office. She has a sedentary job as an administrative assistant. Nancy has two grown children; her elderly mother moved in 3 months ago, and Nancy is now responsible for her care. Nancy is concerned about having to pay for extra medical expenses as her husband recently lost his job. Nancy has not seen her primary care physician (PCP) recently, but now goes for a 6-month follow-up visit. Her PCP had previously started Nancy on lifestyle modification (diet and exercise), metformin, and simvastatin.



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Current Treatment Regimen

- Metformin 850 mg daily
- Simvastatin 40 mg daily
- Aspirin 81 mg daily

Health History

- Hyperlipidemia diagnosed 1 year ago
- T2DM diagnosed 1 year ago
- Former smoker (quit 2 years ago; was a 1 pack/day cigarette smoker)
- Diet: Reports that she tries to limit fat intake, has decreased consumption of high-sugar sweets to twice a week, and has wine with dinner on weekends
- Limited exercise mainly on weekends and walks associated with shopping
- Family history: Her mother has a history of CVD; her father, diagnosed with T2DM, died of a heart attack at 65 years of age

Laboratory Results

Laboratory Tests	Current Visit	Previous Visit
Glycated hemoglobin (A1C)	7.5%	7.30%
Fasting plasma glucose (FPG)	135 mg/dL	120 mg/dL
LDL-C	118 mg/dL	180 mg/dL
High-density lipoprotein (HDL)	47 mg/dL	49 mg/dL
Fasting triglyceride levels	182 mg/dL	205 mg/dL

Current Visit

Physical Exam

- Weight 175 lb
- Height 5 ft 4 in
- Body Mass Index (BMI) 30
- Blood Pressure 125/80 mm Hg

†Not an actual Welchol® patient.

***The effect of Welchol® on cardiovascular morbidity and mortality has not been determined.**

Please see Important Information about Welchol® on page 7.

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Clinical Discussion

Clearly, Nancy's A1C and LDL-C levels have not improved enough since her last visit to her PCP. The American College of Cardiology Foundation (ACCF) and the American Diabetes Association (ADA) Consensus Statement states that a patient classified as having T2DM has a high risk for CVD: the stated goal is LDL-C <100 mg/dL, and a patient having at least one additional risk factor is at highest risk for CVD and has a stated goal LDL-C <70 mg/dL.¹ Nancy's A1C level has increased to 7.5% despite starting on metformin; the ADA and the American Association of Clinical Endocrinologists/American College of Endocrinology (AAACE/ACE) have recommended goals for A1C as <7% and ≤6.5%, respectively; both societies recommend goals for A1C as close to normal as possible and the need to individualize to minimize risk of hypoglycemia.^{2,3} Nancy's LDL-C levels have improved, but are still too high at 118 mg/dL. Her HDL cholesterol level is 47 mg/dL, and her fasting triglycerides are 182 mg/dL. She is obese with a BMI of 30.0; her FBG level increased to 135 mg/dL. Nancy's PCP increases

her metformin to 1000 mg twice a day, and her simvastatin to 80 mg/day.

Three Months Later

Three months later on this regimen, Nancy's A1C level is at 7.1%, her LDL-C is now at 108 mg/dL, and her triglycerides are at 180 mg/dL. Nancy's current weight is 165 pounds, and her BMI has gone down to 28.3. Given the fact that her glucose and lipid levels are still not at goal, a consultation with an endocrinologist is made.

Endocrinologist Consultation

The endocrinologist considers how to intensify Nancy's treatment as she is not at goal for her lipid and glucose levels. Nancy is already at the upper limit of the recommended dosage for simvastatin, so going beyond 80 mg is not an option; neither is increasing the dose of metformin. Nancy would like to keep the cost of any new medications to a minimum. The endocrinologist considers adding glimepiride, which would be cost-effective. However, with an A1C of 7.1%, she is at risk for hypoglycemia. Adding a dipeptidyl peptidase IV (DPP-IV) inhibitor and Zetia® (ezetimibe) could help improve both glucose and LDL-C levels with low risk of hypoglycemia; however, it would

require two expensive co-pays imposed by her health plan to obtain these branded medications*. The endocrinologist reviews the risk-benefit ratio of these agents, with minimal potential of inducing hypoglycemia and liver effect, with Nancy. However, Nancy tells him that she cannot pay for two brand medications. After further consideration, the endocrinologist recommends that Nancy consider taking one drug that could reduce both her A1C and LDL-C levels. He explains that Welchol® (colesevelam HCl) reduced both A1C and LDL-C in clinical studies, and there was no significant increase in body weight. He explains to Nancy that Welchol® may lower both her LDL-C and her A1C without being systemically absorbed, and she will only have to pay one branded co-pay. Nancy was given the choice of the two approved Welchol® formulations, 6 tablets that she can take all at once, or as 3 tablets twice daily, or she can take the once daily Welchol® for Oral Suspension, which is mixed with 4-8 ounces of water.

There are several good reasons for prescribing Welchol® in Nancy's case. Her hyperglycemia and primary hyperlipidemia are still not under control after 1 year of therapy. She is concerned

Table. Suggested Treatment Goals in Patients With CMR and Lipoprotein Abnormalities¹

	LDL cholesterol (mg/dL)	Goals Non-HDL cholesterol (mg/dL)	ApoB (mg/dL)
Highest-risk patients, including those with 1) known CVD or 2) diabetes plus one or more additional major CVD risk factors*	<70	<100	<80
High-risk patients, including those with 1) no diabetes or known clinical CVD but two or more additional major CVD risk factors or 2) diabetes, but no other major CVD risk factors*	<100	<130	<90

*Other major risk factors (beyond dyslipoproteinemia) include smoking, hypertension, and family history of premature CAD.

ApoB=Apolipoprotein B; CAD=coronary artery disease; CMR=cardiometabolic risk; CVD=cardiovascular disease.

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*Cost data do not demonstrate clinical significance or that one product is safer or more effective than another.

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about controlling her CVD risk, but she is worried about accruing more co-pays than is necessary. She is pleased to hear that the safety of Welchol® (colesevelam HCl) has been established through an extensive clinical trial program; for more than 9 years, it has been an approved treatment option for patients with high LDL-C levels, and it is available in a formulation for oral suspension. Nancy's endocrinologist informs her PCP of the change he has made and returns her to his care for follow-up and long-term management.

Three Months After the Endocrinology Consultation

Three months later, Nancy's laboratory values show she is now closer to goal (see testing results below), and therapy will continue.

• LDL-C	91 mg/dL
• Triglycerides	192 mg/dL
• A1C	6.6%

Comment

Risk factors for T2DM and CVD often cluster and include obesity, insulin resistance, hyperglycemia, dyslipidemia, and hypertension.¹ The AACE/ACE Consensus Statement and the ADA guidelines for T2DM agree that intervention should be early, intensive, and stringently focused on maintaining glycemic levels as close as possible to the nondiabetic range without causing side effects.^{2,3} Setting individual goals for A1C levels in patients is dependent on a number of factors, including family history, presenting symptoms, age, comorbidities, and duration of disease.¹ A consensus statement from the ADA and the ACCF (Table on page 2) recommends treatment goals for lipid lev-

els in patients with cardiometabolic risk (CMR).¹

New Treatment Regimen With Add-On Therapy

Welchol® is indicated as an adjunct to diet and exercise to reduce elevated LDL-C in patients with primary hyperlipidemia as monotherapy, or in combination with a statin. Welchol® is also indicated as an adjunct to diet and exercise to improve glycemic control in adults with T2DM (not studied as monotherapy).⁴ Welchol® has been used as an oral tablet since its approval in 2000. The most recent formulation, and the one prescribed for Nancy, is Welchol® for Oral Suspension taken once a day mixed with 4-8 oz of water. Adverse events reported in ≥2% of patients in clinical trials with Welchol® were constipation, nasopharyngitis, dyspepsia, hypoglycemia, nausea, and hypertension. Welchol® is not systemically absorbed and is the only agent currently approved by the US Food and Drug Administration for treating both primary hyperlipidemia and hyperglycemia in adult patients with T2DM.

The safety and efficacy of Welchol® in reducing A1C and LDL-C levels have been demonstrated in clinical trials in combination with a sulfonylurea, metformin, and insulin.⁵⁻⁷ Patients in the metformin study had significant reductions in A1C (-0.54%; $p < 0.001$). Welchol® also reduced mean LDL-C. Welchol® should not be used in patients with bowel obstruction, those with serum triglyceride (TG) concentrations of >500 mg/dL, or with a history of hypertriglyceridemia-induced pancreatitis. While not seen in the metformin study, TG levels signifi-

cantly increased in patients taking insulin or a sulfonylurea. TG levels should be monitored.

Treatment Goals for Nancy

- Continue lower calorie diet for further weight loss
- Increased physical activity
- Consultation with her diabetes educator on a regular basis

Conclusion

Welchol® is a safe and effective add-on therapy to metformin and simvastatin, when A1C and LDL-C levels are not at recommended goals.

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Colesevelam Hydrochloride for Management of a Patient With Type 2 Diabetes Mellitus and Primary Hyperlipidemia

Key Point: Welchol® (colesevelam hydrochloride) is indicated for lowering hemoglobin A1C in adult patients with type 2 diabetes mellitus (T2DM) and lowering low-density lipoprotein-cholesterol (LDL-C) in patients with primary hyperlipidemia. This is an important add-on choice for patients with elevated A1C and LDL-C as it provides an option to treat both disorders with one medication. The effect of Welchol® on cardiovascular morbidity and mortality has not been determined.

Alice† is a 63-year-old Caucasian woman who works at her local hospital as a case manager. She presents to her primary care physician (PCP) 7 months after her last visit. Her PCP has the latest reports from her cardiologist to keep him updated on her cardiovascular health. She reports no exertional chest pain, and a recent stress echocardiogram showed normal wall motion with apical dyskinesis and an ejection fraction of 55%. Alice's PCP does a thorough workup to determine her overall health status.



Peter H. Jones, MD, FACP

Current Treatment Regimen

- Atorvastatin 10 mg daily (2004)
- Aspirin 81 mg daily (2007)
- Lisinopril‡ 10 mg daily (2007)
- Metformin 1000 mg at bedtime (2008)
- Low fat diet
- Exercise for 20 minutes 3 times per week

Health History

- Myocardial infarction 2 years ago
- T2DM diagnosed 1 year ago
- Dyslipidemia diagnosed 5 years ago
- A family history of T2DM and coronary heart disease (CHD)

Laboratory Results

	Last Visit (7 months ago)	Current Visit
Glycated hemoglobin (A1C)	6.6%	7.1%↑
Fasting plasma glucose (FPG)	115 mg/dL	125↑
Low-density lipoprotein-cholesterol (LDL-C)	97 mg/dL	100↑
High-density lipoprotein-cholesterol (HDL-C)	45 mg/dL	45
Triglycerides (TG)	210 mg/dL	215↑
Total cholesterol (C)	184 mg/dL	188↑
Non-high-density lipoprotein-cholesterol (non-HDL-C)	142 mg/dL	151↑
Aspartate aminotransferase/alanine aminotransferase (AST/ALT)	WNL	WNL
WNL=within normal limits.		

Clinical Discussion

Alice's outstanding health issues are her rise in A1C and LDL-C levels since her last visit to her PCP 7 months ago. Alice's A1C level has gone up from 6.6% to 7.1% despite her treatment with metformin for 1 year, and she has a rise in her LDL-C level. The recommended LDL-C goal by the American Diabetes Association/National Cholesterol Educational Program Adult Treatment Panel III/American College of Cardiology Foundation (ADA/NCEP ATP III/ACCF) consensus statement is <70 mg/dL for an individual with high cardiometabolic risk (CMR)¹; Alice's LDL-C level of 108 mg/dL is not consistent with current National Cholesterol

Educational Program Adult Treatment Panel III (NCEP ATP III) guidelines for patients at high risk of CHD.² Alice followed a regimen of diet, exercise, and weight loss, but she feels a recent family trip to Italy lessened her resolve to stick to her regimen; she is still overweight with a BMI of 29 kg/m².

A review of Alice's current treatment regimen shows that she was first placed on

Current Visit Exam Findings

- Height 5 ft 4 in
- Weight 163 lb
- Body Mass Index (BMI) 29 kg/m²
- Waist 35 in
- Blood Pressure (BP) 126/76 mm Hg
- Heart Rate 68 beats per minute (BPM)
- Cardiac exam Normal
- Peripheral pulses Normal and no edema

†Not an actual Welchol® patient.

‡Welchol® has not been studied with lisinopril.

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atorvastatin (20 mg daily) in 2004 for dyslipidemia. After Alice had a myocardial infarction in 2007, she was started on low dose aspirin (81 mg daily), and lisinopril (10 mg daily) was added to lower her blood pressure. Most recently, metformin (1000 mg at bedtime) was added in 2008. Metformin is the first-line drug for the treatment of T2DM, particularly in overweight people; it is the most commonly prescribed oral antidiabetes agent.^{3,4}

Since Alice is in the highest risk category for CHD and is not at goal for LDL-C or A1C levels, her PCP returns her to the cardiologist to further manage her care.

Cardiologist Visit

First and foremost, Alice's cardiologist wants to reduce Alice's LDL-C and A1C levels to goal. According to the NCEP ATP III guidelines, a LDL-C goal <70 mg/dL and a non-HDL-C goal <100 mg/dL are preferred recommendations for a patient such as Alice.⁵ The American Heart Association and the American College of Cardiology (AHA/ACC) guidelines for secondary prevention state that these goals are reasonable, rather than optional, targets.⁶

Because of these guidelines, the cardiologist wants to further reduce Alice's LDL-C level. After careful consideration, the cardiologist decides that the best option is to switch Alice's treatment plan from atorvastatin 10 mg/day to atorvastatin 40 mg/day to achieve at least an additional 12%-14% reduction in her LDL-C level.⁷ He also decides to add Welchol® (colesevelam HCl) 3.75 gm/day because he would like to reduce her LDL-C level by another 15%-20%, as well as reducing her A1C level by an additional 0.5%.⁸⁻¹⁰

The cardiologist could have considered other options, such as switching Alice to rosuvastatin 20 mg/day and/or adding ezetimibe (to reduce her LDL-C level), increasing her metformin dosage to 2000 mg/day, and/or considering the addition of a dipeptidyl peptidase IV (DPP-IV)

inhibitor (to reduce her A1C level); none of these options would provide the dual benefits of reducing both her LDL-C and A1C levels with one agent. In addition, prescribing Welchol® would eliminate a branded co-pay for an additional drug. Welchol® is available as 625 mg tablets; she can take 6 all at once, 3 tablets twice daily, or a once-daily Welchol® Oral Suspension, which can be mixed with 4-8 ounces of water. Alice decides to take the oral suspension as she has difficulty swallowing tablets.

Three Months After Visiting the Cardiologist

Three months later, Alice's laboratory values demonstrate a marked improvement in her cholesterol and glucose levels:

- LDL-C 69 mg/dL ↓
- HDL-C 47 mg/dL ↑
- Non-HDL-C 120 mg/dL ↓
- A1C 6.6% ↓

Add-On Therapy With Welchol® for Patients With T2DM and CHD

The addition of a bile acid sequestrant (BAS) to a statin has long been recognized as a safe and effective way to lower LDL-C levels by an additional 20% to 25%. A clinical trial by Hunninghake and colleagues demonstrated that adding colesevelam hydrochloride 3.8 g to atorvastatin 10 mg resulted in a 48% mean reduction from baseline in LDL-C level, with demonstrated safety and tolerability.¹¹ T2DM was not an inclusion criterion for this study.

Welchol® is the only BAS that is indicated as an adjunct to diet and exercise to reduce LDL-C and improve glycemic control in adults with T2DM.¹² Welchol® was originally approved in the United States in 2000 as a cholesterol-lowering agent; the US Food and Drug Administration approved Welchol® for use in the treatment of T2DM in 2008. Three pivotal clinical trials were the foundation for

the approval of Welchol® as add-on therapy with other antidiabetes medications, including a combination with metformin, a sulfonylurea, or an insulin-based regimen. The baseline levels of A1C in these trials were in the range of 7.5% to 9.5%.⁸⁻¹⁰ Welchol® was shown to consistently reduce A1C levels in these studies by a mean treatment difference of 0.5% versus placebo, irrespective of the background T2DM treatment regimen. Adverse events reported in ≥ 2% of patients in clinical trials with Welchol® were constipation, nasopharyngitis, dyspepsia, hypoglycemia, nausea, and hypertension. Welchol® should not be used in patients with bowel obstruction, those with serum triglyceride (TG) concentrations of >500 mg/dL, or with a history of hypertriglyceridemia-induced pancreatitis. While not seen in the metformin study, TG levels significantly increased in patients on insulin or a sulfonylurea. TG levels should be monitored.

In Alice's case, the addition of Welchol® to atorvastatin resulted in a 31% reduction over her previous LDL-C level; additionally, Alice had a 0.5% reduction in her A1C level. Welchol® was well tolerated, and Alice did not experience weight gain.

Treatment Goals for Alice

- Compliance with medications
- Continued weight loss
- Consultation with a certified diabetes educator on a more frequent basis
- Practice home glucose monitoring
- More frequent visits with PCP

Conclusion

Based on clinical studies, Welchol® is a safe and effective add-on therapy for adult patients with T2DM who are not at their recommended A1C and LDL-C levels.

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CARDIOLOGY NEWS.

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IMPORTANT INFORMATION ABOUT WELCHOL® (colesevelam HCl)

Indications

Welchol is indicated as an adjunct to diet and exercise to:

- reduce elevated low-density lipoprotein cholesterol (LDL-C) in patients with primary hyperlipidemia (Fredrickson Type IIa) as monotherapy or in combination with an hydroxymethylglutaryl-coenzyme (HMG CoA) reductase inhibitor
- improve glycemic control in adults with type 2 diabetes mellitus

Important Limitations of Use

- Welchol should not be used for the treatment of type 1 diabetes or for the treatment of diabetic ketoacidosis
- Welchol has not been studied in type 2 diabetes as monotherapy or in combination with a dipeptidyl peptidase 4 inhibitor and has not been extensively studied in combination with thiazolidinediones
- Welchol has not been studied in Fredrickson Type I, III, IV, and V dyslipidemias

Contraindications

Welchol is contraindicated in individuals with bowel obstruction, those with serum triglyceride (TG) concentrations of >500 mg/dL, or with a history of hypertriglyceridemia-induced pancreatitis.

Warnings and Precautions

The effect of Welchol on cardiovascular morbidity and mortality has not been determined.

Welchol can increase serum TG concentrations particularly when used in combination with sulfonyleureas or insulin. Caution should be exercised when treating patients with TG levels >300 mg/dL.

Welchol may decrease the absorption of fat-soluble vitamins A, D, E and K. Patients on vitamin supplements should take their vitamins at least 4 hours prior to Welchol. Caution should be exercised when treating patients with a susceptibility to vitamin K or fat-soluble vitamin deficiencies.

Caution should also be exercised when treating patients with gastroparesis, gastrointestinal motility disorders, major gastrointestinal tract surgery, and when treating patients with dysphagia and swallowing disorders. Welchol reduces gastrointestinal absorption of some drugs.

Drugs with a known interaction with colesevelam (glyburide, levothyroxine, and oral contraceptives [ethinyl estradiol, norethindrone]) should be administered at least 4 hours prior to Welchol. Drugs that have not been tested for interaction with colesevelam, especially those with a narrow therapeutic index, should also be administered at least 4 hours prior to Welchol. Alternatively, the physician should monitor drug levels of the co-administered drug.

To avoid esophageal distress, Welchol for Oral Suspension should not be taken in its dry form.

Due to tablet size, Welchol for Oral Suspension is recommended for, but not limited to, any patient who has difficulty swallowing tablets.

Phenylketonurics: Welchol for Oral Suspension contains 48 mg phenylalanine per 3.75 gram packet.

Adverse Reactions

In clinical trials, the adverse reactions observed in $\geq 2\%$ of patients – and more commonly with Welchol than placebo – regardless of investigator assessment of causality seen in:

-Adults with Primary Hyperlipidemia were: constipation (11.0% vs 7.0%), dyspepsia (8.3% vs 3.5%), nausea (4.2% vs 3.9%), accidental injury (3.7% vs 2.7%), asthenia (3.6% vs 1.9%), pharyngitis (3.2% vs 1.9%), flu syndrome (3.2% vs 3.1%), rhinitis (3.2% vs 3.1%) and myalgia (2.1% vs 0.4%)

-Adult patients with Type 2 Diabetes were: constipation (8.7% vs 2.0%), nasopharyngitis (4.1% vs 3.6%) dyspepsia (3.9% vs 1.4%), hypoglycemia (3.0% vs 2.3%), nausea (3.0% vs 1.4%) and hypertension (2.8% vs 1.6%)

Post-marketing experience: Due to the voluntary nature of these reports it is not possible to reliably estimate frequency or establish a causal relationship:

-Increased seizure activity or decreased phenytoin levels have been reported in patients receiving phenytoin concomitantly with Welchol.

-Reduced International Normalized Ratio (INR) has been reported in patients receiving warfarin concomitantly with Welchol.

-Elevated thyroid-stimulating hormone (TSH) has been reported in patients receiving thyroid hormone replacement therapy.

Pregnancy

Welchol is Pregnancy Category B.

