

STRATEGIES
BEYOND
STATINS FOR
CONTROL OF
DYSLIPIDEMIAS

Care Gap: Reaching Guideline Goals

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Care Gap: Reaching Guideline Goals

Over the course of the last two decades, a series of landmark multicenter placebo-controlled trials with HMG CoA reductase inhibitors (statins) established that reductions of serum low-density lipoprotein cholesterol (LDL-C) provide substantial reductions in the risk of cardiovascular (CV) events. Increasingly rigorous LDL-C targets were established in treatment guidelines as evidence gathered from large trials correlated greater relative risk reductions with greater relative LDL-C reductions. These studies have brought the current targets to levels that may be difficult to achieve with statin monotherapy, particularly among the highest-risk patients with the greatest likelihood of a CV event. While statins are generally safe, the proportion of patients who do not tolerate drugs in this class increases with increasing doses. The care gap produced by an inadequate response or intolerability to statins leaves patients vulnerable to preventable events. It is appropriate to consider strategies beyond statins to place patients at treatment goals.

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Treatment Targets: The Increasing Care Gap

In patients at risk for a cardiovascular (CV) event, there may be no incremental reduction in low-density lipoprotein cholesterol (LDL-C) achievable with current therapy that does not lead to an incremental further reduction in risk. Several major studies have associated more intensive versus less intensive LDL-C lowering with increased protection against CV events including PROVE-IT,⁽¹⁾ TNT,⁽²⁾ SEARCH,⁽³⁾ and IDEAL.⁽⁴⁾ These and other trials have also provided reassurance that low levels of LDL-C are safe. In the TNT trial, which provided an impressive demonstration of the principle that lower is better in patients with established CV disease, there appeared to be a continuous proportional relationship between lower LDL-C and lower rates of events across every stratification up to and including <1.03 mmol/L, which was the lowest stratification evaluated.⁽⁵⁾ Although only 11% of the study population achieved LDL-C levels this low, and the relative risk reduction over the next stratum, those with a level between 1.03 and 1.55 mmol/L, did not reach statistical significance, the slope of the correlation between LDL-C and risk remained consistent. There was no evidence of any increase in adverse events that correlated with LDL-C reductions. In the Cholesterol Treatment Trialists meta-analysis of 14 cholesterol-lowering therapy trials in 18,686 patients with diabetes, there was a significant 21% proportional reduction in major vascular events per mmol/L reduction.⁽⁶⁾

Data such as these have been included in the recently revised Canadian Cardiovascular Society (CCS) guidelines, which have set aggressive targets for patients with established CV disease as well as for those at moderate risk of experiencing their first CV event.⁽⁷⁾ The LDL-C target, which should be pursued in all high-risk patients, is ≤ 2.0 mmol/L or a 50% reduction in LDL-C from baseline. The same target is appropriate in intermediate risk patients if the baseline LDL-C is ≥ 3.5 mmol/L. If the LDL-C is lower in the intermediate-risk group, the same LDL-C targets should be considered if ApoB is ≥ 1.2 g/L or if non-HDL-C is ≥ 4.3 mmol/L. The trigger for lipid-lowering treatment in low-risk patients is an LDL-C ≥ 5.0 mmol/L except in individuals with familial hypercholesterolemia who should be treated at any LDL-C level. The evidence to support lipid lowering even in low-risk patients includes a meta-analysis conducted by the Cholesterol Treatment Trialists.⁽⁸⁾ In data pooled from 27 trials with statins, this analysis stratified patients by 5-year major CV event risk. A significant risk reduction was observed for all groups, including those with less than a 10% estimated 5-year risk for an event. In the JUPITER trial which recruited otherwise healthy patients with an elevated C-reactive protein (CRP) level, a marker of elevated CV risk, highly significant CV risk reduction

accompanied median LDL-C reductions even though patients were required to have LDL-C <3.35 mmol/L at entry (Table 1)⁽⁹⁾.

TABLE 1 | 2012 Canadian CCS Summary of Treatment Target Guidelines

Risk level	Initiate therapy if	Primary Target LDL-C	Alternate Target
High	Consider treatment in all (Strong, High)	≤ 2 mmol/L or $\geq 50\%$ decrease in LDL-C (Strong, High)	Apo B ≤ 0.8 g/L Non HDL-C ≤ 2.6 mmol/L (Strong, Moderate)
Intermediate	LDL-C ≥ 3.5 mmol/L (Strong, Moderate) Consider if Apo B ≥ 1.2 g/L or Non-HDL-C ≥ 4.3 mmol/L (Conditional, Moderate)	≤ 2 mmol/L or $\geq 50\%$ decrease in LDL-C (Strong, High)	Apo B ≤ 0.8 mg/L Non HDL-C ≤ 2.6 mmol/L (Conditional, Moderate)
Low*	LDL-C ≥ 5.0 mmol/L Familial hypercholesterolemia (Strong, Moderate)	50% reduction in LDL-C (Strong, Moderate)	

*for those in the 6-9% group, consider yearly calculation of Framingham Risk Score and discussion about risk-benefit ratio of pharmacotherapy at lower levels of LDL-C.

Adapted from Anderson TJ, et al. As presented during Canadian Cardiovascular Congress (CCC) 2012.

Although statins have proven instrumental in establishing the value of intensive lipid lowering, and are the preferred therapeutic modality, the CV benefits appear to be related to the magnitude of LDL-C reduction and may be independent of which treatment strategy is used to reach the target. In the Cholesterol Treatment Trialists analysis, for example, the correlations between LDL-C lowering and CV risk reduction were consistent without regard to treatment arm. Despite the fact that the vast majority of prospective data linking LDL-C reductions to protection from CV risk was performed with a statin therapy, other sets of data, including epidemiologic studies,⁽¹⁰⁾ suggest that low LDL-C provides CV protection no matter how it is achieved. For this reason, most guidelines, including those issued by the CCS, recommend targets independent of therapeutic strategy, while emphasizing that statins are the preferred initial treatment in light of the accumulated evidence. While lifestyle modifications, such as low cholesterol diet or greater exercise, may exert cardioprotective effects independent of lipid lowering, pharmacologic options, including bile acid sequestrants, cholesterol absorption inhibitors, and fibrates are also recommended in order to reach targets not achieved on statins and lifestyle modifications alone. These alternatives are essential substitutes in those who do not tolerate statins.

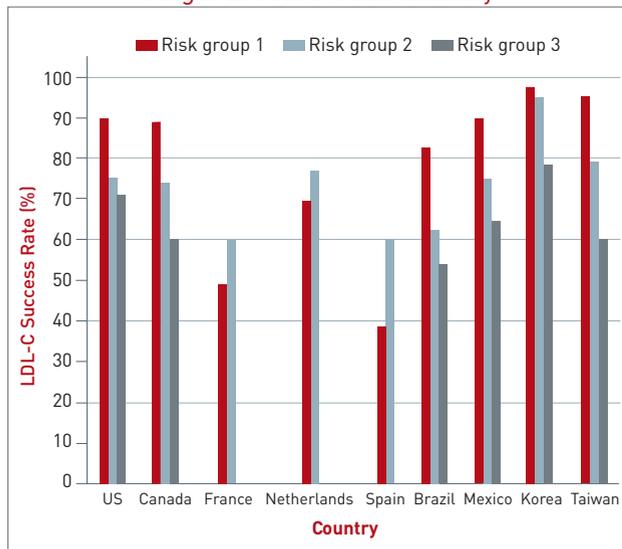
Barriers to Reaching Treatment Targets

In surveys to determine the proportion of patients on lipid-lowering therapies who are reaching LDL-C goals, the targets of the therapy are increasingly stringent according to risk which explains the

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higher rate of high-risk patients relative to low-risk patients not reaching treatment goals. For example, in an international survey of nine countries that included Canada, 86% of low risk, 74% of moderate risk, and 67% of high-risk patients were at goals defined by cholesterol management guidelines.⁽¹¹⁾ With an overall 67.3% of treated patients at goal, Canada was below the median 73% success rate, ranking fifth against a high of 83.5% in Korea and a low of 47.4% in Spain (Figure 1). However, the authors noted that overall control rates had climbed steeply, despite more rigorous goals, since a similar survey published in 2000.⁽¹²⁾

FIGURE 1 | Proportion of Patients Reaching LDL-C Target Levels in each Country



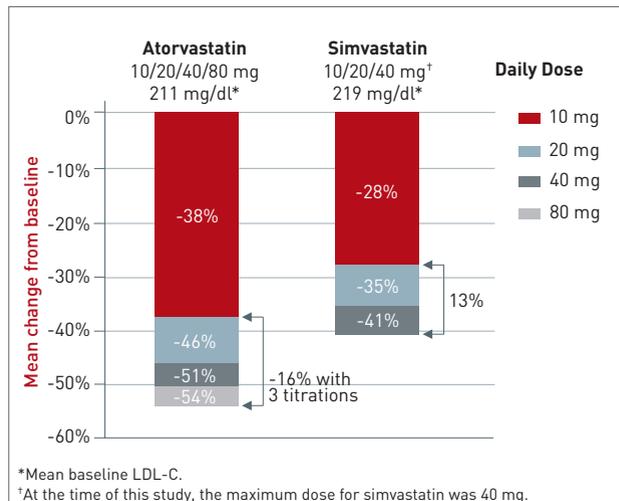
Adapted from Waters D et al. *Circulation*. 2009;120:28-34

The reasons for lower success rates in patients at greater risk cannot be wholly attributed to more stringent goals. In Canada, the LDL-C target is the same in those with high and moderate risk. For many patients whose high risk is defined by Framingham Risk Score (>20% estimated 10-year risk defines high risk), the elevated baseline LDL-C levels are more difficult to bring to the target range with standard doses of statin monotherapy. Although the LDL-C lowering effect per milligram of any specific statin varies, all agents in this class provide their greatest lipid lowering effect at the lowest recommended dose (Figure 2).⁽¹³⁾

Higher doses provide relatively modest further reductions in LDL-C, averaging 5% to 7% each time the dose is doubled. For high-risk patients with a high baseline level, large doses of statins may still be insufficient to bring LDL-C to goal.

Even if statin doses can be raised high enough to reach LDL-C treatment goals, several obstacles remain. Several initiatives, including one in Canada,⁽¹⁴⁾ have been developed to identify patients who required higher starting doses in order to accelerate the titration process. Another is that the

FIGURE 2 | Majority of LDL-C Lowering Occurs at the Lowest Statin Dose



Adapted from Jones P et al. *Am J Cardiol* 1998;81:582-587.

risk of adverse events increases with intensive-dose therapy.⁽¹⁵⁾ While it is estimated that 10% to 15% of patients on chronic statin therapy experience some form of muscle-related symptoms,⁽¹⁶⁾ The U.S. Food and Drug Administration (FDA) has required labeling for some statins that includes a black-box warning about the potential for severe myopathies at the highest doses. In the effort to avoid these adverse events, many physicians may be unwilling to titrate statins beyond moderate dose levels even when patients remain short of goals.

Intolerance to statins is typically described in relative terms. Absolute contraindications, such as hepatotoxicity and rhabdomyolysis are rare.⁽¹⁷⁾ The prevalence of myalgias in routine use of statins is difficult to estimate. In patient surveys and post-marketing studies, rates of myopathies are lower than in clinical trials.⁽¹⁸⁾ This suggests many such complaints captured when patients are asked about specific side effects are not significant in daily practice. However, even subtle side effects may influence adherence rates. Defined as taking >80% of medication, adherence rates at one year were approximately 50% in one Canadian study.⁽¹⁹⁾ Not surprisingly, poor adherence is associated with an increased risk of CV events.⁽²⁰⁾ Again, as side effects are dose-related, the higher doses needed to reach treatment targets may limit adherence and the advantage of seeking recommended goals.

Strategies to Reach LDL Targets

Bringing LDL levels to target is essentially never an isolated goal in patients at risk for CV events. Statins are the first-line pharmacologic therapy for individuals with elevated LDL-C, but these agents are not the first step in treatment. Although clinicians may give limited attention to lifestyle modifications because of the difficulty involved in enlisting patients to make these changes, regular exercise and a healthy diet can have an important

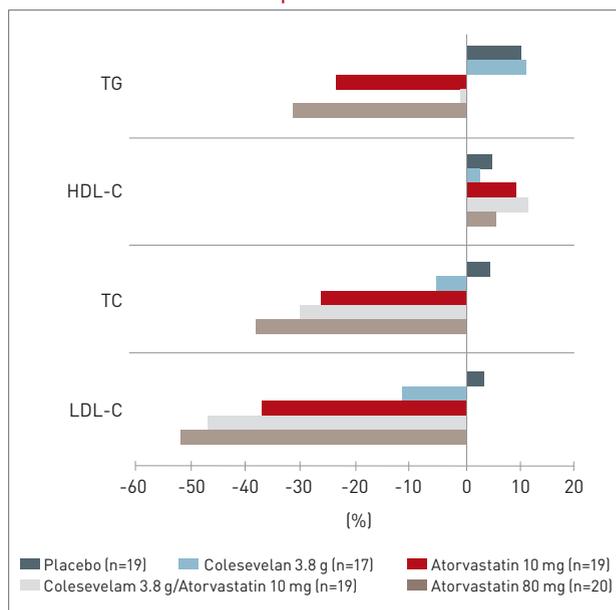
favorable impact on a host of CV risk factors^[21] at the same time that produce improvements in LDL-C as well as other lipid subfractions.^[22] It is essential that lifestyle changes be emphasized and pursued even if a well-tolerated regimen of a statin monotherapy is effective at bringing patients to the LDL-C target.

Statins are identified in the CCS guidelines as first-line therapy for the treatment of elevated LDL-C due to their efficacy, their tolerability, and their proven ability to reduce CV events in large trials. However, in those not able to reach treatment goals with lifestyle changes and a well-tolerated dose of statin monotherapy, the treatment goals should still be pursued with adjunctive pharmacotherapies. The alternatives with the greatest impact on LDL-C are the cholesterol absorption inhibitor ezetimibe and bile acid sequestrants. When added to a statin, both types of agents provide a further LDL reduction ranging from 10% to 20%. In a placebo-controlled trial, bile acid sequestrants were the first to associate a reduction in LDL-C with a reduction in CV risk.^[23] Comparable data are not available for ezetimibe. Both drugs are well tolerated. Bile acid sequestrants are associated with constipation. However, this risk is lower with second generation colestevlam relative to the first generation agents cholestyramine and colestipol (Figure 3).^[24]

Statins have been instrumental in defining the goals of LDL-C lowering, but it is important to recognize that they are not the only avenue for achieving these goals. In the CCS guidelines, as in other major guidelines, reaching the target is considered essential for providing optimal protection against CV events. The tight correlation between LDL-C and risk of events provides the rationale for pushing through to the treatment goal even if multiple therapies are needed.

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FIGURE 3 | Adding Bile Acid Sequestrant to Standard Daily Regimen: Improvements in Serum Lipids



Adapted from Hunninghake D et al. *Atherosclerosis* 2001;158:407-416

Conclusion

Despite the efficacy of statins for lowering LDL-C, there is a significant and persistent care gap in reducing the risk of CV events through the treatment of dyslipidemias. In those intolerant to statins or who do not reach goals on statins alone, other methods of reducing LDL should be pursued. While other dyslipidemias and other CV risk factors should be addressed aggressively, the overwhelming evidence that link LDL-C targets to a reduction in CV risk justifies particular urgency for considering treatments beyond statins when statins alone are not enough to bring the patient to goal. ●

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Bile Acid Sequestrants: Rediscovering an Alternative to Statins

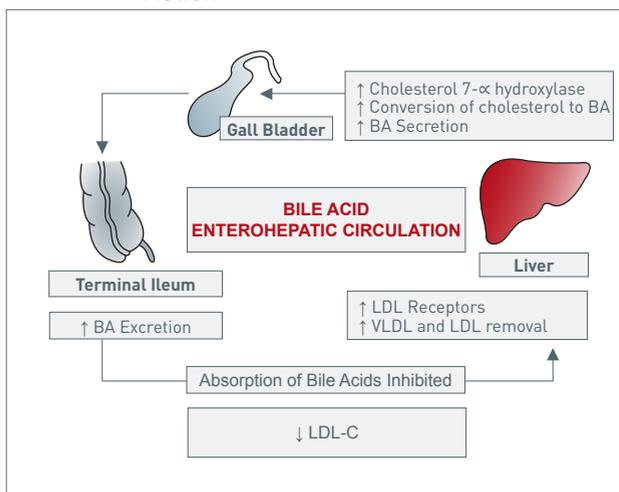
Bile acid sequestrants have been employed in the treatment of dyslipidemias for nearly 50 years. Over the past two decades, their role has been overshadowed by HMG CoA reductase inhibitors (statins), which produce larger reductions in low-density lipoprotein cholesterol (LDL-C) levels and have been more extensively studied in multinational clinical trials. However, bile acid sequestrants can offer substantial reductions in LDL-C making them an appropriate substitute in patients who cannot tolerate statins and an adjunctive therapy in patients who are not reaching treatment goals on statins alone. The lipid-lowering mechanism of bile acid sequestrants, which is now understood in detail that was not available when these agents were first shown to reduce cardiovascular (CV) events, is complementary and additive to that of statins. Newer formulations of bile acid sequestrants may make this class of drug more convenient and better tolerated.

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Mechanism of Action

Bile acid sequestrants were the first agents to demonstrate that pharmacologic reductions in low-density lipoprotein cholesterol (LDL-C) can reduce cardiovascular (CV) events. In 1964, they were the first pharmacologic agent to receive regulatory approval for this indication. Their mechanism is dependent on the important role played by bile acids in cholesterol homeostasis. Bile acids are released from the gallbladder after a meal into the gastrointestinal tract to aid digestion.^[1] Normally, about 95% of bile acids are reabsorbed in the terminal ileum and returned to the liver through the enterohepatic circulation. Replenishment of lost bile acids is performed by hepatocytes, which synthesize bile acids from cholesterol. When bile acid sequestrants inhibit the absorption of bile acids and their return through the enterohepatic circulation, the cholesterol pool in the liver becomes depleted as the liver directs more cholesterol towards synthesis of bile acids to keep up with their loss into the large intestine. As a result, LDL receptor expression on hepatocytes is upregulated to draw cholesterol from the circulation. The upregulation of the LDL receptor is considered the key final common pathway for removing cholesterol from the circulation.^[2] This lowers both total cholesterol and LDL-C (Figure 1).

FIGURE 1 | Bile Acid Sequestrants: Mechanism of Action



The activity of bile acid sequestrants differs from that of the cholesterol absorption inhibitor ezetimibe, which blocks the Niemann-Pick C1-like 1 (NPC1L1) receptor, a central mediator of cholesterol uptake by enterocytes in the upper small intestine (duodenum and jejunum).^[3] As a result, ezetimibe prevents cholesterol absorption at the brush border of the upper small intestine. The final result is depletion of the liver cholesterol pool and upregulation of the LDL receptor in order to increase LDL particle uptake and replenish the cholesterol in the liver. However, in contrast to bile acid sequestrants, ezetimibe is absorbed through the gastrointestinal (GI) tract and is extensively metabolized to an active phenolic

glucuronide which reaches the systemic circulation after oral administration.^[4] Bile acid sequestrants are not absorbed and their distribution is limited to the GI lumen.^[5] However, both classes of intestinal drugs – cholesterol absorption inhibitors and bile acid sequestrants – ultimately upregulate hepatocyte LDL receptors and this results in increased LDL particle uptake and decreased plasma levels of LDL.

Once thought to be relatively inert, bile acids also seem to have endocrinologic functions that affect several digestive and metabolic processes.^[6] They have a significant role in the regulation of GI motility, they mediate water and electrolyte absorption, and they influence nutrient absorption. More recently, they have been shown to influence glucose metabolism to a sufficient degree that bile acid sequestrants have been extensively evaluated as an adjunctive treatment in type 2 diabetes mellitus (DM2).^[7] The mechanism of the beneficial effect on glycemia is not fully understood, but is thought to be mediated through incretins or via incretin-like effects.

The three bile acid sequestrants available for clinical use are cholestyramine, colestipol and colesevelam. The basic mechanisms of these agents for lowering plasma cholesterol are comparable, but there are structural differences that alter bile acid binding activity and side effect profile. Cholestyramine and colestipol are considered first-generation agents, while colesevelam, a second-generation agent, has greater bile acid binding affinity and greater potency on a milligram basis than the other two. All of the most common side effects of bile acid sequestrants, including flatulence, dyspepsia, and diarrhea, have been lower on colesevelam than on cholestyramine.^[8-9] In particular, colesevelam is not associated with significant constipation.^[10] In addition, while first-generation agents impaired uptake of a broad range of drugs, such as propranolol, thiazide diuretics and penicillin, such drug interactions have not been reported for colesevelam. Not least important, colesevelam, unlike other bile acid sequestrants, which are produced in powder form, is available in a tablet formulation.

Clinical Trials: Efficacy and Safety

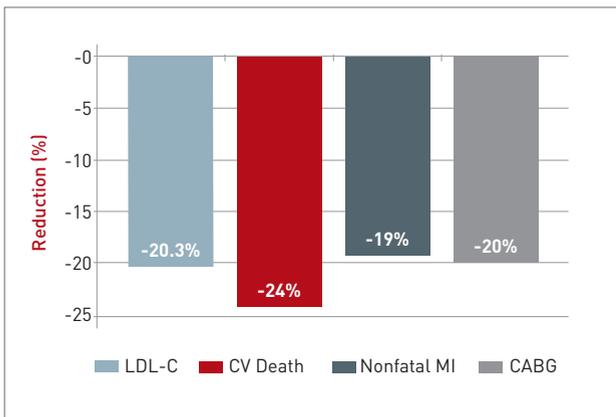
Clinical trials have demonstrated benefits of bile acids sequestrants on CV outcomes, lipid profile, and atherosclerosis as assessed by non-invasive imaging. The more recent evidence of a beneficial effect on glycemic control may have relevance to CV risk as well as prevention of the complications of diabetes.

The earliest major clinical trial to demonstrate primary prevention of major adverse CV events (MACE) was the Lipid Research Clinics Coronary Prevention Trial (LRCCPT), which compared 24 g per day of cholestyramine to placebo in 3806 men with risk factors for CV disease.^[12] The average LDL-C

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reduction from baseline was 20.3% over the duration of the study. Over a mean duration of 7.4 years, the rate of fatal and non-fatal myocardial infarctions (MIs) among those randomized to the bile acid sequestrant was 19% lower than in the group given placebo. It is notable that this reduction in events was achieved despite relatively poor compliance that reduced the average daily dose to 14 g per day. A correlation was subsequently shown between amount of drug taken, degree of LDL-C lowering, and risk reduction (Figure 2).

FIGURE 2 | LRCCPT: Reductions in the Primary Prevention of Major Adverse CV Events



Adapted from The Lipid Research Clinics Coronary Primary Prevention Trial results. I. Reduction in incidence of coronary heart disease. *JAMA* 1984;251(3):351-64.

Further with respect to atherosclerotic events, an abstract presented at the 2012 American Diabetes Association (ADA) Scientific Meeting used a national healthcare claims database to link at least 6 months adherence to colessevelam with a significant reduction in CV events among patients with DM2 (Ye X, et al. ADA 2012, Abs 939-P). Given the limitations of this type of observational study of a database, the results were nonetheless consistent with the reduction of atherosclerotic events seen with cholestyramine in LRCCPT. Of course, prospective confirmation of this benefit in a randomized clinical trial is needed.

Bile acid sequestrants were also employed in some of the earliest studies that demonstrated an association between reductions in LDL-C and stabilized or even improved atherosclerotic plaque burden on angiography. In the NHLBI Type II Coronary Intervention Study, 119 patients were placed on a low-cholesterol diet and then randomized to 24 g/day of cholestyramine or placebo.^[13] At the end of 5 years of treatment, there was a 65% reduction in atherosclerotic plaque progression from baseline in those randomized to the bile acid sequestrants relative to placebo.

These studies were followed by a series of angiographic studies that showed an association between LDL-C reduction and altered progression of atherosclerosis. For instance, in the Cholesterol Lowering

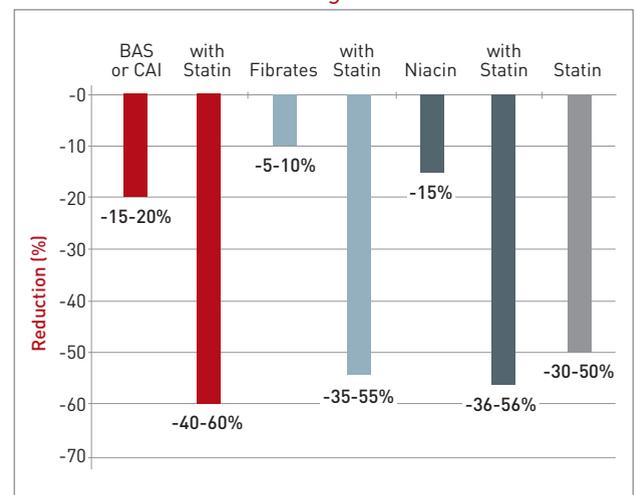
Atherosclerosis Study (CLAS I),^[14] the follow-up CLAS II study,^[15] and the Familial Atherosclerosis Treatment Study (FATS),^[16] there were consistent reductions in progression and increases in regression of plaques on coronary angiograms in those receiving active therapy compared to those receiving placebo. In CLAS I, the active therapy was a combination of colestipol and niacin which reduced LDL-C by approximately 40% and increased high-density lipoprotein cholesterol (HDL-C) by more than 35%. In FATS, colestipol was combined with lovastatin to produce a 46% reduction in LDL-C and a 15% increase in HDL-C. Other regression studies with a bile acid sequestrant alone, such as the St. Thomas Atherosclerosis Regression Study (STARS),^[17] which employed cholestyramine, also contributed to evidence that LDL-C reductions slow or even reverse atherosclerotic disease.

Finally, with respect to glycemic control, several small studies have associated bile acid sequestrants alone or in combination with anti-diabetic agents with favorable effects in patients with DM2. For instance, in a 6-week, placebo-controlled crossover study with cholestyramine, the bile acid sequestrant was associated with a 13% reduction in fasting glucose and a 0.5% reduction in HbA1c.^[18] Similar results were achieved with a pilot study of colessevelam and supported by a subsequent meta-analysis of 8 additional colessevelam studies.^[19-20]

Guidelines: Role of Bile Acid Sequestrants

Statins remain the first-line treatment for control of LDL-C in all major guidelines. Numerous studies have confirmed the efficacy of this class of agents in reducing both LDL-C and risk of CV events (Figure 3). However, adjunctive and alternative agents are often needed to reach current treatment goals and for patients who are unable to tolerate appropriate statin doses. Of those placed on statin monotherapy, approximately one third may not reach treatment goals, especially with increasingly strict recommended target levels of LDL-C.^[21] In addition, there is a small but substantial rate

FIGURE 3 | LDL-C Lowering



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of statin intolerance, variably estimated between 5% and 10% in clinical practice.^[22] Effective and safe alternatives to statins are needed in this situation as well.

In those who require alternative or adjunctive agents beyond diet and other lifestyle changes to reach goals, the choices include bile acid sequestrants, the cholesterol absorption inhibitor ezetimibe, fibrates and niacin. While more than one of these agents may be appropriate in any specific individual, accompanying CV risk markers might be one factor to influence the choice of a specific agent. For example, bile acid sequestrants increase triglycerides, suggesting fibrates may be a more appropriate choice in patients with significant hypertriglyceridemia. Niacin, which can induce flushing even with controlled release formulations, is widely considered appropriate for patients with depressed HDL-C levels. However, the Atherothrombosis Intervention in Metabolic Syndrome with Low HDL/High Triglycerides (AIM-HIGH) study was unable to show a reduction in CV events despite a median 20% increase in HDL-C and a median 16% reduction in LDL-C,^[23] introducing controversy about the role of extended release niacin in CV risk reduction in patients already on statin therapy. Bile acid sequestrants and ezetimibe offer the specific reductions in LDL-C. Event reductions proven with bile acid sequestrants as monotherapy have never been shown with ezetimibe as monotherapy. Both bile acid sequestrants and ezetimibe, however, offer complementary and additive LDL-C reduction when combined with a statin and can help patients reach their LDL-C targets. Due to their favorable effect on glucose metabolism, bile acid sequestrants may be particularly attractive in patients with DM2 when triglyceride control is not problematic.

Compliance and Bile Acid Sequestrants

Since the time they were introduced, statins were seen as a substitute for bile acid sequestrants not only because they offered more potent lipid lowering but because they were better tolerated. However, the side effects associated with bile acid sequestrants are typically mild, while the benefits from reducing LDL-C to target are potentially substantial in patients who are not at target or who are intolerant to statins. Considering strategies that will induce patients to remain compliant with these agents is of course critical to the delivery of their clinical benefits (Figure 4).

FIGURE 4 | Bile Acid Sequestrants

	Cholestyramine	Colestipol	Colesevelam
LDL-C Lowering	15% to 20%	15% to 20%	15% to 20%
Common side effects	Modest rates of GI side effects such as constipation, flatulence and dyspepsia	Modest rates of GI side effects such as constipation, flatulence and dyspepsia	Low rates of GI side effects, such as flatulence and dyspepsia
Efficacy demonstrated for glucose lowering	No	No	Yes
Formulation	Powder	Powder	Tablet

Adapted from Bays H, Jones PH. *Vasc Health Risk Manag* 2007;3(5):733-42.

While GI complaints are generally the most prominent adverse events with all bile acid sequestrants, the greater relative tolerability of the second-generation agent colesevelam has been associated with high rates of compliance, reaching 93% in one study, which was comparable to the rate of compliance seen with placebo.^[9] The availability of colesevelam as a tablet is also convenient for dosing. Both features may influence the decision in selecting a bile acid sequestrant to combine with other therapies, including statins, because of the critical role of long-term adherence in deriving benefits.

Conclusion

The clinical value of bile acid sequestrants in achieving LDL-C goals in selected patients should not be overlooked. Although the linear relationship between reductions in LDL-C and the protection from CV events was primarily demonstrated with statins, guidelines suggest that the LDL-C target can be attained with other agents when statin monotherapy is insufficient. Due to the stringent target LDL-C levels specified in recent lipid guidelines, adjunctive therapies are increasingly required. As an adjunctive or alternative therapy, bile acid sequestrants can be useful for helping patients at risk attain these LDL-C targets. Their lipid-lowering effect is complementary to that provided by statins. By increasing the proportion of patients who attain LDL-C targets, bile acid sequestrants have the potential to further reduce the risk of preventable CV events. ●

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STRATEGIES BEYOND STATINS FOR CONTROL OF DYSLIPIDEMIAS

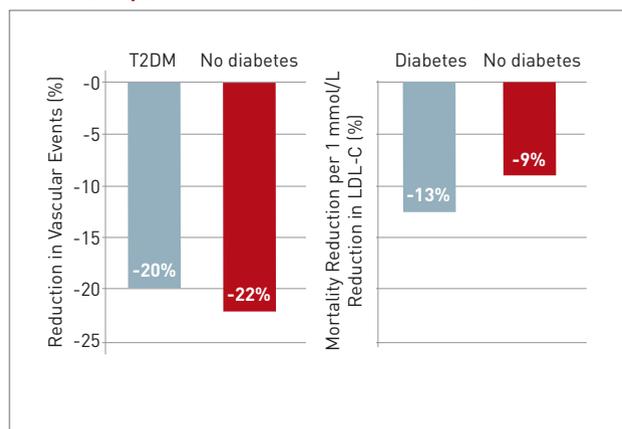
**Dyslipidemia in Patients with
Type 2 Diabetes: Special Challenges**

Cardiovascular (CV) disease accounts for a large proportion of the excess and premature mortality related to type 2 diabetes mellitus (DM2). In relation to age-matched individuals, people with DM2 are 2 to 3 times more likely to have a CV event than age-matched people without diabetes.⁽¹⁾ According to data from the Canadian Diabetes Association (CDA), approximately 80% of patients with DM2 die of CV disease or stroke, which is a rate that is 2 to 4 times greater than in patients without diabetes.⁽²⁾ Optimal protection from CV events depends on tight control of the major risk factors that are commonly identified in patients with DM2, including hyperlipidemia and hypertension in addition to hyperglycemia. Of these risk factors, hyperlipidemia deserves particular attention. Data from several studies, including UKPDS, support the premise that tight control of lipids, relative to tight control of other risk factors, provides the greatest relative protection against CV events.⁽³⁾ In the STENO-2 trial, there was a 57% relative reduction in CV events observed among those reaching treatment goals for lipids, blood pressure, and blood glucose relative to those who did not,⁽⁴⁾ but the authors reported that reaching lipid targets may have provided the greatest relative contribution to risk reduction.

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HMG-CoA reductase inhibitors (statins) are the first-line pharmacologic therapy for reaching guideline recommended goals for low-density lipoprotein cholesterol (LDL-C). In the large statin trials that included type 2 diabetes mellitus (DM2) patients, post-hoc analyses suggest that the highly favorable risk-to-benefit ratio, including an all-cause mortality benefit, has been at least as large in those with DM2 as those without (Figure 1).^[5] In many major guidelines, including those newly issued by the Canadian Cardiovascular Society (CCS),^[6] the presence of DM2 is considered an indication for seeking the most aggressive LDL-C goals. Perhaps due to the difficulty of reaching these low levels, the proportion of patients with DM2 at target is low.^[7-8] Strategies to increase the proportion of DM2 patients at treatment goals have major implications for risk reductions.

FIGURE 1 | 26 Trials: Value of More vs. Less Statins



Adapted from Goldfine AB et al. *N Engl J Med* 2012; 366:1752-1755

Statins are effective and generally well tolerated, but it is important to recognize that these agents are not the only pharmacologic tool for lipid lowering, particularly when confronted with patients with DM2 who cannot reach treatment goals on statins alone. While other lipid-lowering agents, such as

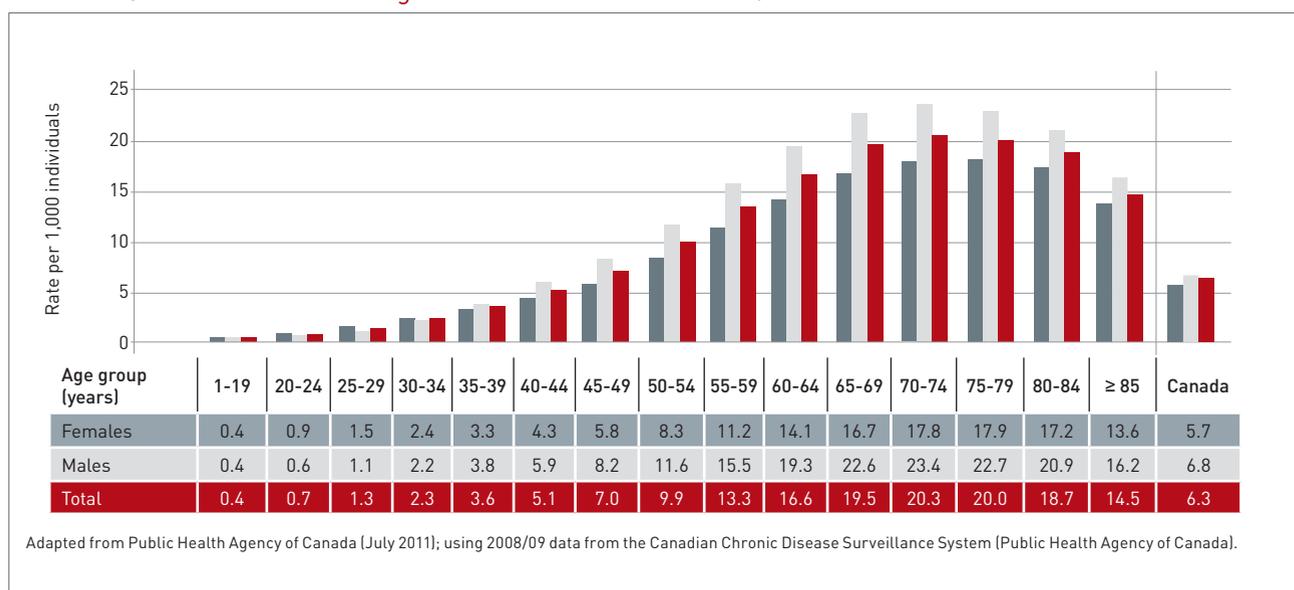
bile acid sequestrants, lipid absorption inhibitors, and fibrates are typically employed in the small proportion of patients who are intolerant to statins, it is important to consider adjunctive use of these agents in those who cannot reach treatment goals on statins alone or at a dose of statin that is acceptably tolerated. The frequency with which patients with DM2 remain above treatment goals represents a large missed opportunity to reduce the rate of cardiovascular (CV) events.

Epidemiology of Lipid Abnormalities in Type 2 Diabetes

The prevalence of diabetes is on a steep upwards trajectory. Between 2010 and 2030, there will be an estimated 70% increase in the number of adults with diabetes in developing countries and a 20% increase in developed countries.^[9] The age- and sex-adjusted diabetes prevalence in Canada will increase by 40%, from 6.8% in 2010 to 9.9%, or 3.4 million in 2020! A majority of these people have type 2 diabetes and many of whom have dyslipidemia, which is characterized by elevated plasma triglyceride levels, low levels of high-density lipoprotein cholesterol (HDL-C), and small, dense atherogenic LDL particles. Although statins are efficacious in patients with type 2 diabetes, rates of CV events remain elevated in such patients even after statin treatment.

Diabetes has turned into an epidemic in industrialized countries driven by the increasing rates of obesity.^[10] In Canada, like the United States,^[11] there has been a corresponding rise in the rates of obesity and diabetes over the past several decades.^[12] The Canadian Diabetes Association (CDA) estimates that 9 million Canadians, or about 25% of the population, now have diabetes or meet the current definition of prediabetes (Figure 2).^[2] Of those with diabetes, approximately 90% have DM2. Further growth in the proportion of the population that is obese and that have diabetes

FIGURE 2 | Incidence rates of diagnosed diabetes: Canada 2008/2009



Adapted from Public Health Agency of Canada (July 2011); using 2008/09 data from the Canadian Chronic Disease Surveillance System (Public Health Agency of Canada).

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is predicted.⁽¹³⁾ This has enormous public health implications. In particular, these trends predict a corresponding rise in cases of myocardial infarction (MI), stroke, congestive heart disease, and other consequences of vascular dysfunction, which are closely correlated with both obesity and DM2.⁽¹⁴⁾

Patients with DM2 typically have multiple risk factors for CV disease, including dyslipidemia and hypertension. A comprehensive approach to CV risk management is therefore appropriate in this population, but dyslipidemias deserve emphasis. Some of the most compelling evidence of CV and stroke risk reduction from intervention directed at a modifiable risk factor has been generated by lipid-lowering studies. The relative benefit has largely been derived from ad hoc analyses of DM2 patients who participated in the major statin trials, but consistency of benefit across trials supports current treatment recommendations, including those from the CCS.⁽¹⁵⁾

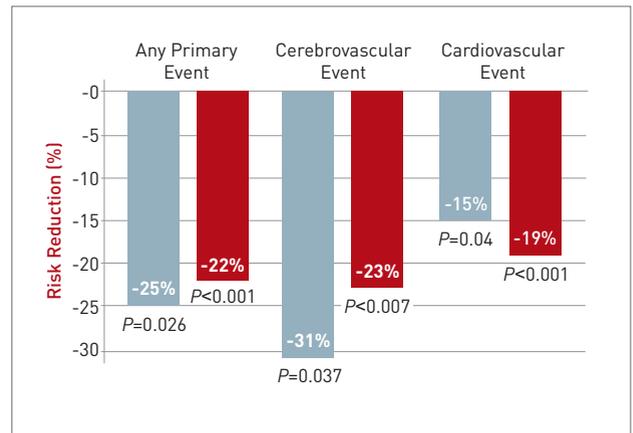
Dyslipidemia in Diabetes

Despite the fact that reaching guideline-recommended LDL-C targets should be considered a priority for CV risk reduction, patients with DM2 do not have higher average LDL-C levels than those without diabetes.⁽¹⁶⁾ However, there is evidence that LDL-C associated with DM2 has greater atherogenicity due to smaller and denser LDL-C particles.⁽¹⁷⁾ It is notable that hypertriglyceridemia and low HDL-C are far more characteristic of the dyslipidemias associated with DM2, but the value of treating these lipid abnormalities is far less well established than lowering LDL-C. This is not to discount the value of reducing elevated triglycerides, which may contribute to the atherogenicity of LDL-C particles,⁽¹⁸⁾ or raising HDL-C, which tend to be inversely related to plasma triglyceride levels,⁽¹⁹⁾ but LDL-C targets are a priority because of the robust evidence that this leads to CV event reductions.

The benefits of lowering LDL-C in patients with DM2 despite baseline levels that would not necessarily warrant therapy in someone without CV risk factors can be derived from large, multinational studies that included diabetics as well as smaller trials limited to patients with diabetes.⁽²⁰⁻²¹⁾ In the TNT study for example, the relative benefit of more aggressive lipid lowering in the 1,501 DM2 patients was essentially the same as that in the 8,500 patients without DM2 (Figure 3).⁽²²⁾

The CV benefits of increasing HDL-C or hypertriglyceridemia in patients with DM2 have been more difficult to show because of the absence of medications that induce a degree of change in these lipid subfractions that is commensurate with the reduction in LDL-C achieved with statins. However, support for considering strategies to lower triglycerides and raise HDL-C can be derived from

FIGURE 3 | TNT Study: Outcomes in Patients with Diabetes



Adapted from Shepherd J et al. *Diabetes Care* 2006;29(6):1220-6.

the strong inverse relationship between HDL-C levels and CV events has been observed in epidemiologic studies.⁽²³⁾ Some mechanistic properties of HDL-C, including a favorable effect on skeletal uptake of glucose, have also been cited among reasons to predict favorable effects from treating this risk factor in patients with DM2.⁽¹⁹⁾ Similarly, the considerable epidemiologic data that link hypertriglyceridemia to CV risk factor⁽²⁴⁾ have also suggested this lipid abnormality should be addressed along with LDL-C.⁽²⁵⁾

Health Behavior and Diet

The best first-line strategy to reduce the threat of DM2 and the risk this disease poses for CV events is to prevent obesity, which is a major source of the increasing rates of DM2 in Canada and elsewhere.⁽²⁶⁾ Controlled trials have demonstrated that lifestyle changes, particularly weight loss, can prevent or delay the onset of DM2.⁽²⁶⁾ However, the relatively modest changes over sustained follow-up underline the difficulty of achieving sustained lifestyle changes in many individuals.⁽²⁷⁾ The potential for weight loss to reverse DM2 has been best demonstrated with a series of studies evaluating the effect of bariatric surgery on this outcome.⁽²⁸⁾

While many patients with DM2 will not be able to achieve the lifestyle changes required to reverse their disease or to reduce lipids and other treatable risk factors to goals, weight loss, increased exercise, and healthier diets should remain a fundamental part of a therapeutic strategy even if pharmacologic agents are required. Such changes may reduce the need for drug therapies and will have broad health benefits, including indirect effects on vascular health from modification of related but independent pathologic processes, such as hypertension.⁽²⁹⁾

Lipid Lowering Goals in Diabetes

Lipid-lowering goals for diabetes have been issued by several organizations, including the CCS and the CDA,^(15,30) as well as professional organizations in the

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United States and Europe.^[31-32] The recommendations vary only modestly. In the 2009 CCS guidelines, diabetes places men over the age of 45 years and women over the age of 50 years in the high risk category. Younger patients with diabetes reach the high-risk category with additional risk factors. In high-risk patients, the LDL-C target is <2 mmol/L or a 50% reduction from the baseline level. Other abnormal lipid subfractions were identified as secondary targets. For HDL-C, the goal was placed in the context of total cholesterol (TC) with a target of a TC/HDL-C ratio of <4.0.

The CDA also identifies LDL-C as the primary target but the 2008 CDA guidelines specifically recommend measuring and monitoring HDL-C, triglycerides, and total cholesterol. Like the CCS, the CDA recommends a TC/HDL-C ratio of <4.0, but further recommends treatment if the triglyceride (TG) level exceeds 10.0 mmol/L. Measuring plasma ApoB is identified as optional, but the CDA sets a target for ApoB of 0.9 g/L. Both the CCS and the CDA recommend that statins be combined with other lipid-lowering agents when statins alone are not adequate to reach targets. The lipid-lowering therapy categories other than statins listed by the CCS are bile acid sequestrants, fibrates, and niacin.

The Need to Treat Beyond Statins

The benefit from statins in DM2 are largely attributable to their ability to lower LDL-C, which have repeatedly been associated with reductions in CV events and stroke in patients with DM2 whether administered for primary or secondary prevention.^[33-35] However, a large proportion of patients will require additional lipid lowering agents to achieve LDL-C levels <2.0 mmol/L or a 50% reduction in LDL-C from baseline. In one representative survey evaluation of almost 10,000 patients in 9 countries, only about two-thirds of high-risk patients, including those with DM2, were at their LDL-C goal.^[36]

In lipid management in DM2, adding a second agent has the potential not only to increase the proportion of patients at the LDL-C goal but may, in some cases, correct other dyslipidemias that are less well addressed with statins alone. There is also some evidence that specific lipid-lowering agents may modestly improve glucose metabolism, a potentially synergistic effect in risk reduction. In addition, combination strategies have the potential to allow lower doses of statins, thereby reducing the risk of side effects, such as myopathy or hepatotoxicity.

The 2009 CCS guidelines, like other major guidelines, list bile acid sequestrants, cholesterol absorption inhibitors, fibrates, and niacin as alternative or adjunctive lipid lowering agents. Of these, niacin has been particularly helpful in raising HDL, although

efforts to link this activity with a reduction in CV events have so far failed,^[37] and the characteristic flushing associated with this agent, although reduced with extended-release formulations, can be poorly tolerated.^[38] Fibrates have been particularly effective for lowering triglycerides, and gemfibrozil specifically was associated with a reduction in CV events in the Helsinki Heart Study.^[39] However, gemfibrozil is not recommended as an adjunct to statins in the 2009 CCS guidelines because of an increased risk of rhabdomyolysis.^[15]

For reducing LDL-C, which deserves the highest priority for preventing CV events in patients with DM2, as well as others with established CV risk, bile acid sequestrants and cholesterol absorption inhibitors are the most attractive adjunctive to statins. Although these agents, particularly bile acid sequestrants, offer little benefit against elevated triglycerides, and only modest benefit against depressed HDL-C, they can provide up to 20% further reduction in LDL-C when added to a statin.^[40] While the only currently available cholesterol absorption inhibitor, ezetimibe, has never been associated with a significant reduction in CV events in a randomized trial when used as monotherapy (SHARP was positive), bile acid sequestrants were the first agent of any kind to associate lipid lowering with a CV event reduction.^[41] Although this study was not conducted in patients with DM2, the mechanism of benefit, which is lowering of LDL-C, would be expected to be applicable to all groups at elevated CV risk. While the bile acid sequestrants cholestyramine and colestipol are associated with substantial GI side effects, the newer agent in this category, colesevelam, has largely replaced these first-generation agents because it is more potent and better tolerated.^[42-44] More importantly from the point of view of risk management in DM2, colesevelam has been associated with favorable effects on glucose metabolism.^[45] In a pooled analysis of three placebo-controlled trials, colesevelam was associated with a 16.5% reduction in LDL-C ($P<0.001$), a 7.6% reduction in ApoB ($P<0.001$), a 0.5% reduction in HbA1c ($P<0.001$), and a 10% reduction in fasting glucose ($P<0.001$) (Table 1).^[46] This effect on glucose has led to the conclusion that colesevelam, which is now available in a tablet that circumvents the problems of taste and preparation of the powdered formulation,^[47] suggests it may be a particularly attractive add-on lipid-lowering agent in diabetic patients who are not at treatment goals on statins alone.^[48]

Summary

Most people with diabetes are at high risk for CV disease and multifactorial interventions are necessary for vascular protection and/or reduction of CV disease risk and events. Statins are first-line drug therapy to lower LDL-C and adjunctive therapy may often be required to achieve target lipid values.

**TABLE 1 | Diabetes Patients on Metformin:
3 Clinical Studies**

Changes on colesevelam relative to placebo	
HbA1c	-0.5%
Fasting Plasma Glucose	-0.41 mmol/L
LDL-C	-16.5%
Total Cholesterol	-5.8%
Non HDL-C	-8.2%
ApoB	-7.6%
Triglycerides	+12.8%

Adapted from Bays HE. *Endocr Pract* 2011;17(6):933-8.

Both cholesterol absorption inhibitors and bile acid sequestrants are effective second-line agents to lower LDL-C. The diagnosis of DM2 confers a high

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risk of CV events. The benefit of lipid lowering in reducing the risk of CV events, including CV-related mortality, is well established in this population. Numerous studies demonstrate that the rigorous LDL-C goals are difficult to reach on statins alone in high-risk populations. Adjunctive agents can increase the proportion of patients at goal while some add-on agents may be useful in addressing other dyslipidemias associated with increased CV risk. Both cholesterol absorption inhibitors and bile acid sequestrants are valuable in helping DM2 patients reach rigorous treatment goals, but the evidence that bile acid sequestrants can favorably affect glucose metabolism make them attractive in this setting. However, all pharmacologic treatments should be added on top of lifestyle changes to address the many concomitant risk factors typically present in DM2 patients, including obesity and hypertension. ●

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