Intensive LDL-C Lowering in Type 2 Diabetes: How Can We Achieve It?

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The optimal management of type 2 diabetes in order to minimize its associated morbidity and mortality remains a significant challenge for healthcare providers. In Canada, statistics from 2005 showed that 5.5% of the population (1.8 million people) had diabetes; the vast majority of these individuals had type 2 diabetes.[1] A more recently published study using the ICES database found that the prevalence of diagnosed diabetes in Ontario had increased from 5.2% in 1994/1995 to 8.8% in 2004/20055—an almost 70% increase over just 10 years.[2] People with diabetes remain at significantly increased risk for cardiovascular (CV) disease, in addition to blindness and end-stage renal disease.

Studies such as the STENO 2 trial[3] have demonstrated that a comprehensive, multifactorial approach will dramatically reduce the macrovascular and microvascular complications of diabetes. In this study, for example, an intensified multifactorial intervention strategy—including aggressive control of LDL-cholesterol (LDL-C), blood pressure (BP), and glucose in addition to the use of renin-angiotensin-system blockers and ASA—was highly effective in reducing the risk of macro- and microvascular complications by about 50% over the eight years of the trial in patients with diabetes and microalbuminuria. After an additional five years of passive follow-up, the multifactorial risk-reduction strategy was associated with a remarkable 46% reduction in total mortality compared to conventional treatment (hazard ratio 0.54; 95% confidence interval 0.32 to 0.89; $p = 0.02$).[4] As a result of this, and similar studies, the 2008 Canadian Diabetes Association (CDA) Clinical Practice Guidelines[5] emphasize the importance of a comprehensive, multifaceted approach to reduce the risk of diabetic complications. All people with diabetes should receive lifestyle modification including the achievement and maintenance of a healthy body weight, healthy diet, regular physical activity, and smoking cessation. In addition, LDL-C should be treated to target (*i.e.*, < 2.0 mmol/L in high-risk patients), BP should be treated with a target of < 130/80 mmHg and glucose levels should be treated with a target A1C of < 7.0% for most patients.

This review focuses on several elements that need to be considered in the management of dyslipidemia for patients with type 2 diabetes: the increased CV risk associated with diabetes; the benefits of lowering LDL-C; the current targets for lipid levels recommended in Canadian guidelines; the care gap that exists in Canada; and the interventions that can be employed to help achieve LDL-C goals.

DIABETES AND INCREASED RISK FOR VASCULAR EVENTS

Multiple studies have highlighted the increased risk for coronary heart disease (CHD) in people with diabetes.[6-8] For example, a recent analysis of the

TABLE I Individuals with Diabetes Considered to be High Risk for CV Events (2008 CDA Guidelines)[5]

- Men aged ≥ 45 years, women aged ≥ 50 years
- Men < 45 years and women < 50 years with ≥ 1 of the following:
  - macrovascular disease (*e.g.,* silent myocardial infarction or ischemia, evidence of peripheral arterial disease, carotid arterial disease or cerebrovascular disease)
  - microvascular disease (especially nephropathy and retinopathy)
  - multiple additional risk factors, especially with a family history of premature coronary or cerebrovascular disease in a first-degree relative
  - extreme level of a single risk factor (*e.g.,* LDL-C > 5.0 mmol/L, systolic BP >180 mmHg)
  - duration of diabetes > 15 years with age > 30 years

Framingham population[8] revealed that the lifetime risk for CHD for a man with diabetes is 67% and for a woman with diabetes is 57%. Nonetheless, although there is no doubt about the increased risk, the concept that diabetes is a "coronary risk equivalent" has not been supported by many studies and it is now recognized that there exists heterogeneity of CV risk within the diabetic population. The 2008 CDA guidelines state that the following individuals with diabetes should be considered at high risk for vascular events: men aged > 45 years and women aged > 50 years.[5] Furthermore, younger patients should also be considered at high risk if they have any of the characteristics listed in Table 1.

BENEFITS OF LOWERING LDL-C

LDL-C has been established as the primary target in the management of dyslipidemia due to the overwhelming evidence—primarily with statin therapy—that reducing LDL-C levels is associated with improved outcomes. A recent prospective meta-analysis of data involving more than 90,000 individuals from 14 statin trials[9] found that every 1 mmol/L reduction in LDL-C was associated with a 23% reduction in major coronary events, regardless of baseline LDL-C. In other words, the lower the LDL-C, the better. A subsequent meta-analysis in people with diabetes showed similar effects.[10] As a result, the authors of the CDA Guidelines state that ". . . the beneficial effects of lowering LDL-C apply equally well to people with and without diabetes."[5]

There have also been large clinical trials of LDL-C lowering that were conducted exclusively among patients with type 2 diabetes. The most compelling of these is the Collaborative Atorvastatin Diabetes Study (CARDS),[11] in which therapy with a statin (atorvastatin 10 mg daily) was evaluated among 2,838 people with type 2 diabetes, no known CHD and a mean baseline LDL-C of only 3.1 mmol/L. All of the patients had at least one other CV risk factor in addition to their diabetes. Over a mean follow up of 3.9 years, the atorvastatin treatment, with its associated mean 2.0 mmol/L reduction in LDL-C, resulted in a 37% relative risk reduction in CV events (Figure 1) and a 48% relative risk reduction in stroke.

TARGETS FOR THE MANAGEMENT OF DYSLIPIDEMIA FOR PEOPLE WITH DIABETES

The 2008 CDA guidelines' lipid targets for individuals with diabetes at high risk for CVD are consistent with the recommendations published in 2006 by the Canadian Cardiovascular Society (CCS)[12] for other high-risk populations. It is emphasized that LDL-C be used as the primary lipid target, with a goal of 2.0 mmol/L or lower for those at high risk (which the authors describe as "most people with diabetes").[5] In addition to the LDL-C target, both the CDA and the CCS recommend a secondary target of the total cholesterol to high-density-lipoprotein cholesterol ratio (TC:HDL-C) of less than 4.0. This goal, which is considered more difficult to achieve, should only be targeted once the LDL-C goal has been met.[4] Strategies to improve the ratio include lifestyle changes (weight loss, physical activity, smoking cessation), in addition to pharmacotherapy.

DYSLIPIDEMIA CARE GAP IN CANADA

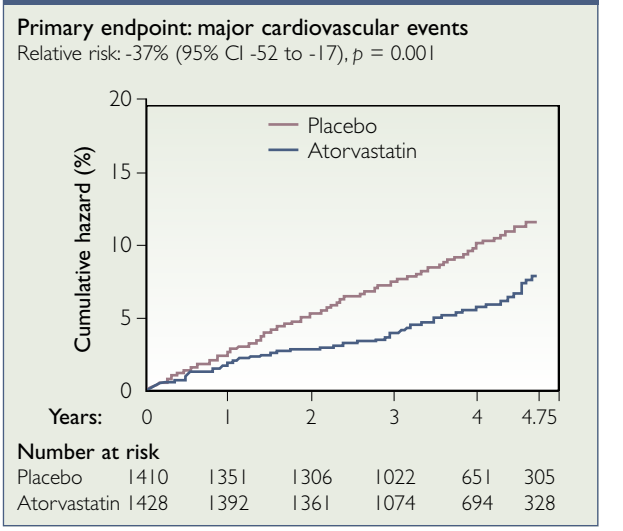
Despite the compelling evidence that LDL-C lowering is associated with reductions in CV morbidity and mortality, and despite the existence of clinical practice guidelines to assist clinicians in treating their patients, there continues to exist a significant care gap for the management of dyslipidemia in Canadian patients. The CALIPSO study[13] published in 2005 showed that, among Canadian patients with dyslipidemia being treated with statins, more than one quarter were not at target LDL-C levels as defined by the 2003 guidelines (LDL-C < 2.5 mmol/L). Of particular note, among those patients deemed to be at high risk (including those with diabetes), 36.4% had not reached their LDL-C targets.

Further evidence exists showing that a substantial portion of patients with dyslipidemia may not be reaching targets, even if they are being treated with medication. In the ACTFAST study,[14] 2,117 patients with dyslipidemia were treated for 12 weeks with algorithm-based statin dosing in an attempt to achieve an LDL-C of less than 2.6 mmol/L. The cohort included 805 patients with type 2 diabetes. Although use of the algorithm did get the majority of these subjects to goal, among subjects who

were already receiving statin therapy at baseline, 41% did not achieve the 2.6 mmol/L target despite titration of their statin dose and the reinforcement of lifestyle interventions. Subjects who were statin-naïve at baseline fared much better: only 20% remained uncontrolled after 12 weeks of therapy.

It should also be noted that, in the CALIPSO and ACTFAST studies, the specified target was higher than the current recommendations for high-risk individuals. With today's more aggressive treatment targets for these individuals, the proportion of patients considered uncontrolled in these studies would have been considerably higher. Indeed, a recent analysis[15] used data from CALIPSO and a meta-analysis of statin studies to estimate the proportion of high-risk patients who would achieve their LDL-C goal of < 2.0 mmol/L if their statin doses were titrated to the maximum dose. It was calculated that, depending on the particular statin used, between 28.2% and 62.7% of high-risk patients would not reach this LDL-C target despite titration to maximum statin dose.

FIGURE 1 **Reduction in Cardiovascular Events with Statin Therapy in the CARDS Trial[11]**



METHODS OF LOWERING LDL-C

Given the ongoing treatment gap in achieving LDL-C targets, it is worthwhile to review the options to lower LDL-C. The CDA guidelines recommend that dyslipidemia be treated with a combination of lifestyle and pharmacologic interventions.

Lifestyle. For patients who are overweight or obese, lifestyle intervention resulting in weight loss of at least 5% to 10% can have a significant beneficial impact on the lipid profile. Dietary modification for these patients should involve a meal plan that is energy-restricted and low in dietary cholesterol, saturated fats, trans fatty acids and refined carbohydrates.[5]

Regular exercise is also an important component of lifestyle modification. Incorporating regular physical activity has been associated with weight loss and may be associated with a reduction in triglycerides and an increase in HDL-C. Finally, smoking cessation is also vital.[5]

Statins. The majority of evidence documenting the benefit of LDL-C lowering has come from trials utilizing statins. These therapies are, therefore, recommended by Canadian and international guidelines as the primary therapy for treating dyslipidemia in patients with or without diabetes. The evidence base for these agents is extensive.

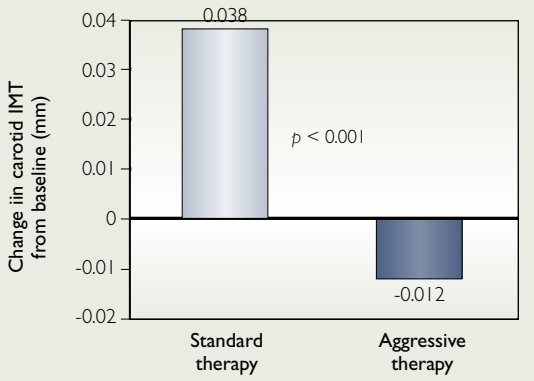
The 2008 meta-analysis of the effect of statin therapy in people with type 2 diabetes included data on 18,686 subjects with diabetes from 14 randomized trials of statin therapy.[10] The investigators calculated that every 1 mmol/L reduction in LDL-C was associated with a 9% proportional reduction in all-cause mortality (p = 0.02) and a 21% reduction in major vascular events in people with diabetes (p < 0.0001).

Combination therapy. Although statin therapy is recommended as the initial pharmacotherapy of choice, many patients still do not achieve their LDL-C goals with such therapy alone. Therefore, if the LDL-C remains above target despite optimally dosed first-line statin therapy, combination therapy with a statin and a second agent, such as a cholesterol absorption inhibitor (ezetimibe), fibrate, or niacin, is recommended.[5]

With respect to ezetimibe, recent evidence has given us additional information as to whether the method of LDL-C lowering influences the degree of clinical benefit. The Stop Atherosclerosis in Native Diabetics Study (SANDS) was a randomized study involving 499 subjects with type 2 diabetes and dyslipidemia.[16] Patients were randomized to be treated with risk-factor interventions aiming for standard LDL-C, non-HDL-C and BP targets, or with risk-factor interventions aimed at more aggressive targets for these parameters. The investigators had previously reported that, compared to baseline, carotid intima-media thickness (IMT) regressed in the aggressive-targets group (LDL-C goal < 1.8 mmol/L) and progressed in the standard-targets group (LDL-C goal < 2.6 mmol/L; -0.012 mm vs. 0.038 mm, respectively; p < 0.001; Figure 2).

Among the group randomized to aggressive goals in SANDS, there was a sizeable subgroup of patients who required the addition of ezetimibe to statin therapy. Of the 223 patients in the aggressive-therapy group eligible for evaluation at the study's end, 69 also received ezetimibe while 154 were receiving statin therapy alone. A subsequent post-hoc analysis compared the IMT out-

FIGURE 2 Aggressive vs. Conventional Lipid and BP Therapy: Effect on Carotid IMT (SANDS trial)[16]



comes in these two groups.[17] It was found that the subjects in the aggressive-therapy group experienced similar reductions in carotid IMT whether they were receiving statin therapy alone or statin plus ezetimibe. The investigators concluded that the addition of ezetimibe appears to be an effective option for patients who are unable to achieve cholesterol goals with statins alone.

The results in this population of patients with type 2 diabetes differ from those of the ENHANCE trial,[18] conducted in a population of patients with familial hypercholesterolemia. In that study, the investigators observed no significant difference in the primary endpoint of mean increase in carotid IMT over two years between patients treated with statin monotherapy and those treated with statin plus ezetimibe, despite a greater mean reduction in LDL-C (58% vs. 41%) in the combination group. It can be argued that the SANDS trial is perhaps more generalizable compared to ENHANCE, since the SANDS patient profile, for example—adults with type 2 diabetes—is a much more common one than the familial hypercholesterolemia of the ENHANCE study. Furthermore, the baseline IMT in SANDS (approximately 0.8 mm) was more typical for an adult population than the approximate 0.7 mm baseline in the ENHANCE population. Finally, the treatment approach used in SANDS was one that is most commonly used in clinical practice: start with lifestyle interventions and statins and, if these prove insufficient, add ezetimibe. The results of the SANDS post hoc analysis are also consistent with a 2005 meta-regression analysis,[19] which revealed similar regression lines for LDL-C lowering vs. CHD events in statin vs. non statin trials.

CONCLUSIONS

A multifactorial risk-reduction strategy must be employed to minimize the risk of complications for people with type 2 diabetes, and reduction of LDL-C to target levels must be an essential component of the strategy. Clinical-trial evidence has demonstrated that, in terms of LDL-C, lower is better: aggressive treatment to an LDL-C < 2.0 mmol/L should be the goal of lipid-lowering therapy. Lifestyle interventions and statin therapy form the two cornerstones of therapy for the reduction of LDL-C. When these are insufficient to reach LDL-C targets, the addition of a second agent, most commonly ezetimibe, should be considered.

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