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2018 Clinical Practice Guidelines

Dyslipidemia

Diabetes Canada Clinical Practice Guidelines Expert Committee

G.B. John Mancini MD, FRCPC, FACC, Robert A. Hegele MD, FRCPC, FACP, FAHA, FCAHS, FCCS, Lawrence A. Leiter MD, FRCPC, FACP, FACE, FAHA

KEY MESSAGES

- The beneficial effects of lowering low-density lipoprotein (LDL)-cholesterol with statin therapy apply equally well to people with diabetes as to those without the disease.
- The primary treatment goal for people with diabetes is LDL-cholesterol consistently <2.0 mmol/L or >50% reduction from baseline. Alternative targets and goals are non-high-density lipoprotein (non-HDL) cholesterol <2.6 mmol/L or apolipoprotein B <0.8 g/L. Achievement of the primary goal may require intensification of healthy behaviour interventions with statin monotherapy. On occasion, the addition of other lipid-lowering medications may be required.

KEY MESSAGES FOR PEOPLE WITH DIABETES

- Most adults with diabetes are at greater risk for cardiovascular diseases, such as heart attack and stroke.
- People with diabetes have an increased risk of cardiovascular diseases even if their LDL-cholesterol is "normal". They have an even higher risk if their LDL-cholesterol is elevated.
- Adults with diabetes should have their cholesterol tested yearly or as indicated by your health-care provider. More frequent testing may be necessary for people taking cholesterol medications.
- Always discuss your cholesterol results with your physician or nurse practitioner and other members of your health-care team.

Introduction

Diabetes is associated with a high risk of vascular disease (i.e. 2- to 4-fold greater risk than that of individuals without diabetes). In fact, cardiovascular disease (CVD) is the primary cause of death among people with type 1 and type 2 diabetes (1–3). Aggressive management of all CVD risk factors, including dyslipidemia, is, therefore, generally necessary in individuals with diabetes (4–6).

The most common lipid pattern in people with type 2 diabetes consists of hypertriglyceridemia (hyper-TG), low high-density lipoprotein cholesterol (HDL-C) and relatively normal plasma concentrations of low-density lipoprotein cholesterol (LDL-C). However, in the presence of even mild hyper-TG, LDL-C particles are typically small and dense and may be more susceptible to oxidation. In addition, chronic hyperglycemia promotes the glycation of LDL-C, and both glycation and oxidation are believed to increase the atherogenicity of LDL-C. Both of these processes may impair function and/or enhance atherogenicity even in those with type 1 diabetes with a normal lipid profile. The risk imparted by this lipid profile, even when LDL-C is considered low, remains quite substantial (7). Table 1 lists the components of dyslipidemia associated with diabetes (8,9). Many of these abnormalities also are seen in people with metabolic syndrome (10,11).

Table 1
Dyslipidemia components associated with type 2 diabetes and metabolic syndrome*

- Increased TG and TG-rich lipoproteins
- Increased postprandial TG
- Low HDL-C
- Low apo A-I
- Decreased small HDL, prebeta-1 HDL, alpha-3 HDL
- Increased apo B
- Increased LDL particle number
- Increased small, dense LDL
- Increased apo C-III
- Increased non-HDL-C
- Increased oxidized and glycated lipids

Apo, apolipoprotein; *HDL*, high-density lipoprotein; *HDL-C*, high-density lipoprotein cholesterol; *LDL*, low-density lipoprotein; *LDL-C*, low-density lipoprotein cholesterol; *TG*, triglyceride.

* Adapted from reference 8.

Risk Assessment of Individuals with Diabetes

A detailed overview of risk assessment to guide decisions in whom to use statin therapy is provided in the Cardiovascular Protection in People with Diabetes chapter, p. S162. Principles of risk assessment also are discussed in the *2016 Canadian Cardiovascular Society (CCS) Guidelines for the Management of Dyslipidemia* (12,13), and efforts were made to ensure consistency between the guidelines. Accordingly, actual risk calculation is not required in most cases as people with diabetes >40 years of age, or >30 years of age and duration of diabetes >15 years or with concomitant microvascular or cardiovascular (CV) disease warrant therapy (13).

Screening

The burden of dyslipidemia is high in people with diabetes. A national cross-sectional chart audit study of 2,473 Canadians with type 2 diabetes revealed that 55% of individuals with a diabetes

Conflict of interest statements can be found on page S183.

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diagnosis of 2 years' duration also had dyslipidemia. This proportion rose to 66% in those with diabetes for 15 years (14). Therefore, a fasting lipid profile (total cholesterol [TC], HDL-C, TG and calculated LDL-C) should be conducted at the time of diagnosis of diabetes and if treatment is not warranted, the assessment should be repeated annually or as clinically indicated. If treatment for dyslipidemia is initiated, more frequent testing is warranted.

A fast of >8 hours may be inappropriate for individuals with diabetes, especially if long-acting basal insulin is part of their treatment regimen. Although nonfasting LDL-C is generally valid unless TG is elevated, non-HDL-C (defined as TC minus HDL-C) or apolipoprotein B (apo B) measurements (see below) are also valid even in the nonfasting state and even if the TG level is not normal. Indeed, the most recent CCS guidelines for management of dyslipidemia now endorse the option of nonfasting lipid measurements more broadly, not solely in people with diabetes, unless the person is known to have abnormalities of TG. Laboratories will not report LDL-C when TG is ≥4.5 mmol/L. In people known to have this level of hypertriglyceridemia, a fasting profile should be performed but non-HDL-C or apo B may still need to be used to determine atherogenicity of the dyslipidemia in this circumstance as well (13). For screening in children and adolescents, please refer to the chapters dedicated to diabetes in these groups (Type 1 Diabetes in Children and Adolescents chapter, p. S234; Type 2 Diabetes in Children and Adolescents chapter, p.S247).

Healthy Behaviour Interventions

Healthy behaviour interventions remain a key component of CVD prevention strategies and of diabetes management in general. Achievement of healthy weight and aerobic activity level, adoption of an energy-restricted, compositionally well-balanced diet that is low in cholesterol, saturated and trans fatty acids and refined carbohydrates, inclusion of viscous fibres, plant sterols, nuts and soy proteins, use of alcohol in moderation and smoking cessation all are fundamental considerations to improve glycemic control, the overall lipid profile and, most importantly, to reduce CVD risk (15–26). Each of these is discussed in more detail in accompanying chapters (Physical Activity and Diabetes chapter, p. S54; Nutrition Therapy chapter, p. S64; Weight Management in Diabetes chapter, p. S124).

LDL-C

A number of studies and meta-analyses have shown that the degree of LDL-C lowering with statins and the beneficial effects of lowering LDL-C apply equally well to people with and without diabetes (27–38). Large trials have demonstrated the benefits of statin therapy in both the primary and secondary prevention of CVD, and subgroup analyses of these studies have shown similar benefits in subsets of participants with diabetes (28–30,39). Across all subgroups, statin therapy provides the same relative risk reduction in terms of outcomes, but the absolute benefit depends on the baseline level of absolute risk, which is typically increased in people with diabetes. Subgroup analyses from statin trials also have shown similar relative benefits of LDL-C lowering, regardless of baseline LDL-C (30,32).

Intensive-dose statin has been demonstrated to improve outcome compared to moderate-dose statins, even in older people with MI or in people on dialysis (40–43). Therefore, statin use should be considered for any person with diabetes at risk of a CV event. In the very small group of lower-risk individuals with type 2 diabetes, the relative reduction in CVD risk with statin therapy is likely to be similar to that seen in those at higher global risk for CVD, but the absolute benefit from statin therapy is predicted to be smaller. However, the global CVD risk of these individuals is lifelong, will increase with age and may be worsened in the presence of additional CV risk factors. Therefore, repeated monitoring of the CVD risk status of people with diabetes (as outlined in the screening section above) is recommended.

The results of the Heart Protection Study (HPS), which compared simvastatin 40 mg daily to placebo, provide considerable insight into the importance of LDL-C lowering in the general population and, in particular, among people with diabetes (31). In the overall study, involving >20,000 participants, similar risk-ratio reductions were observed in participants with baseline LDL-C >3.5 mmol/L, 3.0 to 3.5 mmol/L and <3.0 mmol/L. In the subgroup with diabetes (n=5,963, including 615 people with type 1 diabetes), treatment with 40 mg simvastatin daily resulted in a 27% reduction in CV events and a 25% reduction in stroke relative to treatment with placebo. The risk reduction was similar in the cohorts with and without diabetes, and the treatment benefit was independent of baseline HDL-C and LDL-C levels (LDL-C <3.0 mmol/L or ≥3.0 mmol/L), sex, vascular disease, type of diabetes (type 1 vs. type 2) and A1C level (30). These results emphasized the benefits of statin treatment irrespective of the pre-existing serum LDL-C level.

The Collaborative Atorvastatin Diabetes Study (CARDS) was the first completed statin trial to be conducted exclusively in people with type 2 diabetes without known CVD (32). The mean baseline LDL-C of the study population was 3.1 mmol/L, and all participants had at least 1 CVD risk factor in addition to diabetes. CARDS demonstrated that treatment with atorvastatin 10 mg daily was safe and highly efficacious in reducing the risk of a first CV event, including stroke. Treatment resulted in a mean LDL-C of 2.0 mmol/L and was associated with a reduced risk for CV events and stroke of 37% and 48%, respectively. These study findings support the value of treating even so-called "normal" LDL-C levels in people with type 2 diabetes and no known CVD. This concept is concordant with a recent analysis of CVD risk in adults with diabetes and LDL-C <2.6 mmol/L (7).

As mentioned previously, all CARDS subjects had at least 1 additional CVD risk factor (i.e. history of hypertension, retinopathy, microalbuminuria or macroalbuminuria, or current smoking), a profile that applies to an estimated 70% to 80% of people with type 2 diabetes (32,44). Results from the United States (US) Third National Health and Nutrition Examination Survey (NHANES III) indicate that 82% of people with diabetes and no clinically evident coronary artery disease (CAD) have at least 1 of the CARDS entry criteria risk factors (32). The CARDS investigators concluded that the study findings "challenge the use of a particular threshold level of LDL-C as the sole arbiter of which individuals with type 2 diabetes should receive statin therapy". The absolute risk, determined by other risk factors in addition to LDL-C, should drive the target levels (32,45). Indeed, the investigators questioned whether any individual with type 2 diabetes can be considered at sufficiently low risk for therapy to be withheld (32). A sub-analysis of the Anglo-Scandinavian Cardiac Outcomes Trial—Lipid Lowering Arm (ASCOT-LLA) revealed similar benefits of atorvastatin 10 mg vs. placebo in people with type 2 diabetes, hypertension and at least 3 additional risk factors (46).

The Atorvastatin Study for the Prevention of Coronary Heart Disease Endpoints in Non-Insulin-Dependent Diabetes Mellitus (ASPEN) assessed the effect of atorvastatin 10 mg daily vs. placebo on CVD prevention in 2,410 people with type 2 diabetes (47). Although originally designed as a secondary prevention trial, the protocol underwent several changes, including the addition of participants without known CAD and the eventual conversion of all participants with known CAD to open-label, lipid-lowering medication. Over the 4-year study period, mean LDL-C was reduced by 29% in the atorvastatin group compared to placebo ($p<0.0001$). The composite primary endpoint was reduced by 13.7%; however, this finding was not statistically significant and was generally considered to be