

# Management of Atherosclerosis in Diabetes and the Metabolic Syndrome

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Patients with diabetes or the metabolic syndrome are at increased risk for major atherosclerotic events, such as ischemic myocardial infarction and stroke. To reduce the risk, treatment involves aggressive management of multiple risk factors, including hyperglycemia, hypertension and dyslipidemia. Studies show that ACE inhibitors and statins should be used preferentially in appropriate patients with diabetes or the metabolic syndrome.

by David Lau, PhD, MD, FRCPC

As our media and politicians remind us on a daily basis, Canada's healthcare system is under a great deal of stress, and the stress will continue to grow as time goes on and the population ages. One particularly alarming aspect of the nation's health is the growing prevalence of the interconnected conditions of diabetes and the metabolic syndrome. Both are significant risk factors for progression of atherosclerotic disease and for major cardiovascular (CV) events. As such, the burden these diseases place on our healthcare system is significant and growing.

While every effort should be made to apply effective preventive measures and interventions to reduce the risk of developing the metabolic syndrome or diabetes, the reality is that clinicians must also ensure that those who do develop these conditions receive optimal therapy to reduce their overall risk.

While most clinicians are aware of the effects of interventions on the key markers of risk (*e.g.*, blood pressure [BP], blood glucose and lipids), the effect on the underlying atherosclerotic disease is less well understood. Using clinical trial evidence, this

review examines the effects of various treatment modalities on atherosclerosis in these populations.

Before examining the evidence, a review of definitions and epidemiology is presented.

### Metabolic Syndrome: Definition

The 2003 guidelines of the Canadian Diabetes Association describe the metabolic syndrome as “a highly prevalent, multifaceted condition characterized by a distinctive constellation of abnormalities that include abdominal obesity, hypertension, dyslipidemia, insulin resistance and dysglycemia.”<sup>1</sup>

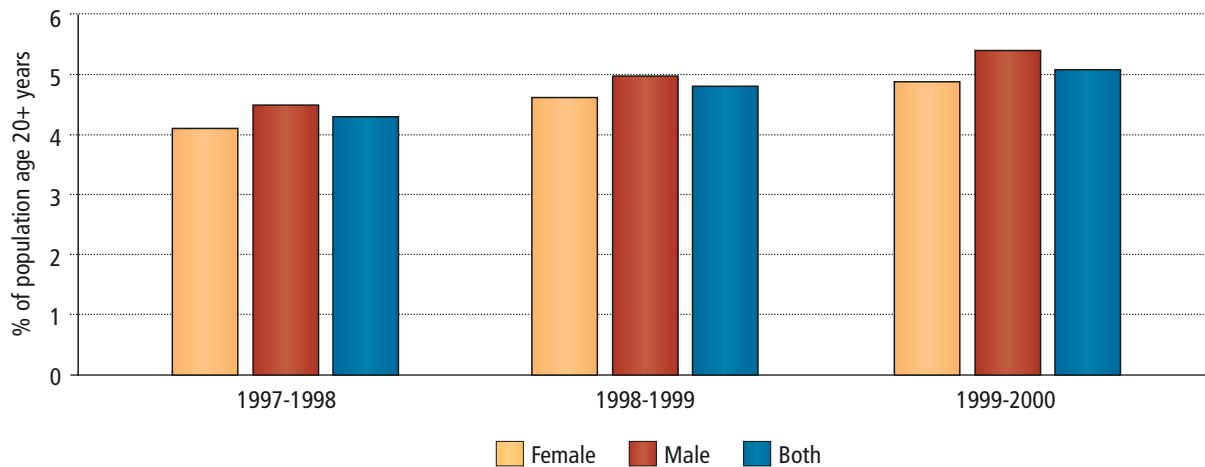
The clearest clinical definition currently in use for the metabolic syndrome comes from the United States' National Cholesterol Education Program. In its third Adult Treatment Panel report (NCEP ATP III), it defines the metabolic syndrome as the presence of at least three of the following:<sup>2</sup>

- waist circumference > 102 cm (men) or > 88 cm (women)
- triglycerides > 1.69 mmol/L
- high-density-lipoprotein cholesterol (HDL-C) < 1.3 mmol/L (men), or < 1.04 mmol/L (women)
- BP > 130/ 85 mmHg
- fasting plasma glucose (FPG) > 6.11 mmol/L

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Figure 1 Prevalence of Diabetes in Canada by Fiscal Year and Sex<sup>3</sup>

\*crude rate per 100 persons aged 20+ years (not age-standardized)

## Epidemiology

The incidence and prevalence of diabetes are steadily on the rise in Canada. Figure 1 shows the increases from the time period of 1997-1998 to 1999-2000, the last period for which data are available.<sup>3</sup> In that year, 5.1% of Canadians over the age of 20 years had a diagnosis of diabetes (1,196,370 individuals). These data, taken from the National Diabetes Surveillance System database, likely underestimate the true prevalence of the disease. Population-based studies, such as the Diabetes Scanning in Canada (DIASCAN) study,<sup>4</sup> suggest that undiagnosed cases bring the total prevalence closer to the neighborhood of 7%.<sup>1</sup>

The metabolic syndrome is far more common. Although there are currently no Canadian data on incidence or prevalence, there are relatively recent American data. The third National Health and Nutrition Examination Survey (NHANES) was a cross-sectional health survey of 8,814 men and women aged 20 years or older in the U.S. conducted from 1988 to 1994. An analysis of this database found the age-adjusted overall prevalence of metabolic syndrome during that period to be 23.7%.<sup>5</sup>

## Impact of Interventions on Atherosclerosis in Diabetes and the Metabolic Syndrome

There are many treatment goals in the management of diabetes, including the prevention of microvascular

complications, such as retinopathy and neuropathy. However, due to the overwhelming numbers of diabetic patients who eventually succumb to CV complications, the primary goal is prevention of CV events.<sup>6</sup> Patients with the metabolic syndrome are also at greatly increased risk for CV events.<sup>7</sup> Because the vast majority of CV events are atherothrombotic in nature, the modification of the atherosclerotic process should be one of the key targets of therapy for these patients. The extent to which various interventions used for diabetes and the metabolic syndrome impact this process is examined below.

**Antihyperglycemic therapy.** To date, trials examining the impact of antihyperglycemic therapies have not demonstrated a direct effect on the atherosclerotic process. The United Kingdom Prospective Diabetes Study (UKPDS), for example, showed that intervention with various antihyperglycemic medications (mostly with agents from the sulfonylurea class) did, in fact, reduce microvascular complications, but had no statistically significant effect on macrovascular events (*e.g.*, myocardial infarction [MI], stroke).<sup>8</sup>

Early mechanistic evidence suggests that the thiazolidinedione (TZD) class of agents (*e.g.*, rosiglitazone, pioglitazone) may have antiatherogenic effects through improved endothelial function and decreased inflammation.<sup>9</sup> These observations have yet to be

## Background Literature Review

**Table 1 Major CV Event Reductions in Diabetic Patients in the HOPE Study<sup>12</sup>**

Endpoint	Event rate (%)		RRR	p
	Ramipril (n = 1,808)	Placebo (n = 1,769)		
CV death+MI+stroke	15.3	19.8	25%	0.0004
MI	10.2	12.9	22%	0.01
Stroke	4.2	6.1	33%	0.0074
CV death	6.2	9.7	37%	0.0001

borne out in clinical studies, but such studies are underway.

The jury is also still out about the role of TZDs in the metabolic syndrome. In a placebo-controlled study of 50 patients, eight weeks of rosiglitazone therapy resulted in an improvement of endothelium-dependent, flow-mediated vasodilation and endothelium-independent, nitroglycerin-induced vasodilation of the right brachial artery. However, the treatment also increased low-density lipoprotein (LDL) cholesterol by 18% and apolipoprotein B by 16%.<sup>10</sup>

**Antihypertensive agents.** The aggressive treatment of hypertension is another one of the key goals of diabetes therapy.<sup>6</sup> The UKPDS examined the impact of tight or less-tight BP control with angiotensin-converting enzyme (ACE) inhibitors or beta-blockers as the primary classes of agents in both treatment groups.<sup>11</sup> Those in the tighter-control group achieved a mean BP of 144/82 mmHg, while those in the less-tight group achieved a mean of 154/87 mmHg. While the numerical difference between the groups was in favor of the tighter control group for all-cause mortality, MI, stroke and peripheral arterial disease (PAD), stroke was the only endpoint whose difference reached statistical significance.

There is benefit to be gained in diabetes strictly from lowering BP, but there are also effects of certain antihypertensives that are independent of BP lowering.

ACE inhibitors, for example, have been shown to greatly reduce CV risk in patients with diabetes. In the Heart Outcomes Prevention Evaluation (HOPE), for example, 3,577 patients with diabetes were enrolled. The investigators found that ramipril therapy significantly reduced the incidence of the combined endpoint of MI, stroke and CV death by 25% in this

**Table 2 Lipid Targets in Patients with Diabetes (2003 Canadian Guidelines)**

Risk level	Targets	
	LDL-C	TC:HDL-C
High (most patients with diabetes)	< 2.5 mmol/L	< 4.0
Moderate*	< 3.5 mmol/L	< 5.0

\*Younger age and shorter duration of diabetes and no other complications of diabetes and no other risk factors for vascular disease

group.<sup>12</sup> Table 1 shows the individual endpoint data for the HOPE diabetic subset.

The investigators of the HOPE study speculated that the beneficial effects in these endpoints for the diabetic population were mediated by mechanisms other than BP reduction. They hypothesized that the benefit came from a protective effect of ACE inhibition on the atherosclerotic process. Among the particular mechanisms cited were a reduction in smooth muscle cell proliferation, stabilization of plaques and prevention of thrombosis. These mechanisms are thought to be the result of the inhibition of the deleterious effects of angiotensin II and a promotion of the beneficial effects of bradykinin.<sup>12</sup>

In the metabolic syndrome, ACE inhibitors may also have a protective role in atherosclerotic disease. A recent placebo-controlled study of the ACE inhibitor quinapril in the metabolic syndrome found that the use of this agent reduced markers of vascular oxidative stress in this population.<sup>13</sup>

Other antihypertensive agents have also been evaluated with respect to reduction of CV risk in patients with diabetes. In the diabetic subgroup of the Losartan Intervention for Endpoint Reduction (LIFE) study of older patients (aged 55 to 80 years) with hypertension, the angiotensin II receptor blocker (ARB) losartan was associated with a 24% relative risk reduction in the primary composite endpoint of CV death, MI or stroke compared to the control agent, atenolol.<sup>14</sup>

Studies in animal models have suggested that anti-atherogenic mechanisms may be behind these benefits.<sup>15,16</sup>

In preliminary trials in the metabolic syndrome, ARBs have demonstrated an improvement in arterial compliance, but no effects on oxidative stress.<sup>17</sup>

**Lipid-lowering therapy.** Along with BP and blood glucose, dyslipidemia is one of the three major modifiable risk factors that should be targeted in a comprehensive approach to diabetes or the metabolic syndrome.

The importance of restoring a healthy lipid balance (in diabetes or the metabolic syndrome, this typically means increasing HDL cholesterol [HDL-C] and lowering triglycerides and LDL cholesterol [LDL-C]) has been shown in many clinical trials and has been underscored by the recommendations in the Canadian diabetes guidelines. For most patients with diabetes, the recommended targets are an LDL-C level below 2.5 mmol/L and a total-cholesterol (TC)-to-HDL-C ratio below 4.0. For the smaller group of patients with diabetes that are at slightly lower risk (younger age, shorter duration of diabetes, no other complications of diabetes and no other risk factors for vascular disease), the targets are less than 3.5 mmol/L for LDL-C and less than 5.0 for the TC:HDL ratio (Table 2).<sup>6</sup>

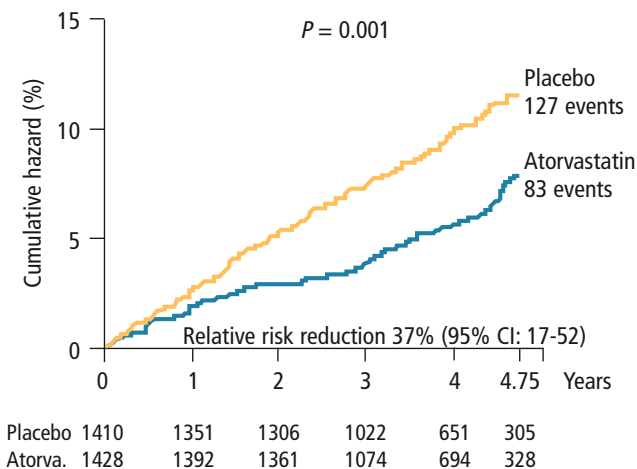
The evidence for statin benefit in diabetes is compelling. The Heart Protection Study (HPS) entry criteria specified that patients had to have coronary artery disease, other occlusive arterial disease or diabetes, with a TC of at least 3.5 mmol/L (average entry TC: 5.9 mmol/L; average entry LDL-C: 3.4 mmol/L).

Of the 20,536 patients, a total of 5,963 had diabetes at baseline.<sup>18</sup> In these patients, treatment with statin therapy (simvastatin 40 mg) was associated with a 22% relative risk reduction vs. placebo in the combined endpoint (major coronary events, strokes, and revascularizations). The protective effect was even more pronounced among patients who did not have a diagnosis of occlusive arterial disease at entry ( $n = 2,912$ ). Even those whose pretreatment LDL-C concentration was below 3.0 mmol/L ( $n = 2,426$ ) had a 27% relative risk reduction with simvastatin vs. placebo.

The benefit of statin therapy on atherosclerotic events has also been shown in the subset of patients with diabetes in the Anglo-Scandinavian Cardiac Outcomes Trial: Lipid-Lowering Arm (ASCOT-LLA).<sup>19</sup> To be included in this trial, patients had to have hypertension and a TC lower than 6.5 mmol/L.

In the prespecified subgroup with diabetes ( $n = 2,532$ ), there was a 23% reduction in the numbers of total CV events in patients treated with atorvastatin 10 mg daily compared to placebo. ASCOT-LLA was halted after 3.3 years of follow-up (five years was specified in the study design) due to the significant benefit in the treatment arm.

**Figure 2 Reduction of CV Morbidity and Mortality in Diabetes with Atorvastatin (CARDS)<sup>20</sup>**



More recently, the results of the Collaborative Atorvastatin Diabetes Study (CARDS) were announced. This large ( $n = 2,838$ ) prospective study was designed to examine the effects of statin therapy on a specific population: patients with diabetes.<sup>20</sup> Apart from type 2 diabetes, patients enrolled in CARDS had no clinical history of coronary, cerebrovascular or severe peripheral arterial disease, an LDL-C of 4.14 mmol/L or lower (baseline average: 3.1 mmol/L) and a TC of 6.78 mmol/L or lower (baseline average: 1.7 mmol/L). In addition, patients had to have one of the following risk factors: hypertension, retinopathy, microalbuminuria/macroalbuminuria or current smoking.

The primary endpoint was a composite of CV morbidity and mortality (acute coronary heart disease death, non-fatal MI, hospitalization for unstable angina, resuscitated cardiac arrest, coronary revascularization and stroke). The investigators found that treatment with atorvastatin 10 mg was associated with a 37% relative risk reduction compared to placebo in the primary endpoint (Figure 2). The primary endpoint results were not significantly different when controlled for age, sex, baseline lipids, baseline systolic BP, retinopathy, albuminuria or smoking. There was also a 27% risk reduction for all-cause mortality in favor of atorvastatin 10 mg. The study was halted

prematurely for ethical reasons, due to the overwhelming benefit of the atorvastatin therapy.

The benefits demonstrated in clinical trials with statin therapy are thought to extend beyond the actual lipid-lowering activity to various pleiotropic effects (*e.g.*, inflammatory, oxidative, and thrombotic).<sup>21</sup>

For example, studies have shown that statins not only significantly reduce the activity of platelet-activating factor, but that the decrease preferentially affects the more atherogenic small, dense LDL particles.<sup>22</sup> Statin therapy has also been shown to increase the activity of lipoprotein lipase (LPL) in patients with diabetes.<sup>23</sup> Low activity of LPL, the enzyme responsible for the removal of triglycerides from the plasma, is associated with atherosclerosis. The authors of a recent review stated that the statin-mediated increase in LPL activity helps to explain the reduction of coronary artery disease (CAD) in diabetic patients treated with statins.<sup>23</sup>

In vitro research has also shown that statins can inhibit the release of natural killer cells, which are also implicated in the pathogenesis of atherosclerosis.<sup>24</sup>

Furthermore, the use of statins can reduce oxidative stress<sup>25</sup> and markers of inflammation,<sup>26-29</sup> which are linked to atherosclerotic progression.

Although no large studies have prospectively examined the role of statins in the metabolic syndrome,


experts have emphatically endorsed their use in patients with this condition due to their direct (lipid-lowering) and indirect (pleiotropic) vascular effects.

Lipid lowering with fibrate therapy has also demonstrated benefit in reducing CV events in patients with diabetes.<sup>33,34</sup>

### Conclusion

Patients with diabetes or the metabolic syndrome are at significantly increased risk for major atherosclerotic events (*e.g.*, ischemic MI, stroke). To reduce this inherent risk, the optimal management of these complicated patients involves aggressive management of multiple risk factors.

The three most well known modifiable targets in these conditions are hyperglycemia, hypertension and dyslipidemia. While successful modification of these risk factors to reach target levels is of benefit in itself, using therapies proven to have other anti-atherosclerotic effects provides the most potent degree of risk reduction.

Studies have shown that certain agents (*e.g.*, ACE inhibitors, statins) exert anti-atherosclerotic effects beyond their primary therapeutic mechanisms. These agents should therefore be used preferentially in appropriate patients with diabetes or the metabolic syndrome. 

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