

# Diabetes and Cardiovascular Disease among Older Adults: An Update on the Evidence

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*The global prevalence of diabetes has increased substantially in recent years, attributable to an increase in new cases and declining mortality. Aging is associated with changes in beta cell function and insulin resistance that predispose to diabetes. Cardiovascular disease is the leading cause of death among older adults with diabetes. In order to reduce the excessive risk of cardiovascular disease, all coronary risk factors must be addressed and treated aggressively. This article will focus on the importance of blood pressure and glycemic control and lipid lowering with statin therapy. Specific considerations in this patient population include high rates of comorbid disease, shorter life expectancy, polypharmacy and falls risk. These factors may alter the therapeutic goals. Treatment should therefore be individualized with consideration given to patient preference and quality of life.*

*Key words: diabetes, cardiovascular disease, older adults, metabolic syndrome*

## Introduction

The global prevalence of diabetes is rising, attributable to an increase in new cases driven by obesity rates and the aging population, and declining mortality.<sup>1</sup> While the prevalence is highest in developed countries, the rise in diabetes rates is greatest in the developing nations.<sup>1</sup> Aging is associated with declining beta cell function, lower blood insulin levels, and increased insulin resistance.<sup>2</sup> One in seven Canadians is over the age of 65 and the proportion of older adults is expected to nearly double over the next 25 years.<sup>3</sup> As the largest segment of our population ages, rates of diabetes are expected to continue rising. From 1995 to 2005, there was a 69% increase in the prevalence of diabetes in Ontario.<sup>1</sup> It is now projected

that by 2010, 10% of the adult population in Ontario will be diagnosed with diabetes and the majority of those will be over 50 years of age.<sup>1</sup>

The older adult population is heterogeneous with wide variations in functional status, comorbidities, and life expectancy. In this article, we highlight the results of studies that included individuals over the age of 65, acknowledging that frail older adults and those at extremes of age are often excluded. Management of diabetes in these persons requires an individualized approach with attention to unique geriatric considerations including cognitive impairment, polypharmacy, and falls risk. Treatment strategies should take into account these factors, as well as quality of life and patient preference.

## Diabetes as a Risk Factor for Cardiovascular Disease

Cardiovascular disease is the leading cause of death among older adults with diabetes.<sup>4</sup> The Cardiovascular Health Study (CHS) showed that individuals over the age of 65 with diabetes were twice as likely to die from cardiovascular disease as their nondiabetic counterparts.<sup>5</sup> This is particularly significant given that cardiovascular disease is already the leading cause of death in people over 70. This study confirms that the deleterious effect of diabetes on cardiovascular mortality seen in the general population persists into older age and emphasizes the importance of intensive management of cardiovascular risk factors among older adults.

## Beyond Glycemic Control: Other Risk Factors

The Steno-2 trial established that, among younger people with type 2 diabetes and microalbuminuria, intensified multifactorial target-driven intervention with tight glucose regulation and the use of renin-angiotensin system blockers, acetylsalicylic acid, and lipid-lowering agents, reduces the risk of vascular complications and mortality.<sup>6,7</sup> Although no studies have specifically addressed this issue in older adults, conditions such as hypertension and dyslipidemia are common in older people, and their treatment is associated with cardiovascular risk reduction.<sup>8,9</sup> For any person with diabetes, glycemic control is only one component of management. A combination of behaviour modification and pharmacologic therapy is appropriate. As interdisciplinary interventions have been shown to improve glycemic control in older adults with diabetes, these individuals should be referred to a diabetes health care team.<sup>10</sup>

## The Metabolic Syndrome

The metabolic syndrome is a multifaceted disorder defined by the coexistence of certain conditions including abdominal obesity, hypertension, dyslipidemia, and fasting hyperglycemia, each of which is an independent risk factor for cardiac

disease (see Table 1).<sup>12-15</sup> There is controversy over whether the metabolic syndrome confers an additional cardiovascular risk beyond the sum of its constituent parts. The metabolic syndrome affects a great number of people and its prevalence increases with age.<sup>11</sup> According to the third National Health and Nutrition Examination Survey (NHANES) approximately 22% of Americans met the ATP III criteria for metabolic syndrome. Prevalence rose from 6.7% among participants aged 20 through 29 to 43.5% and 42% among participants age 60 to 69 and over 70 years of age, respectively.<sup>11</sup>

Approximately one-third of patients in the Cardiovascular Health Study met criteria for the metabolic syndrome.<sup>16</sup> The increased mortality in these patients was confined to those with elevated fasting glucose levels / diabetes or hypertension (defined as a blood pressure greater than or equal to 135/85 mmHg or treatment with blood pressure medications). People with the metabolic syndrome without elevated fasting glucose or hypertension did not have a significantly increased risk of cardiovascular mortality. Those with both had an 82% higher mortality compared with those who did not have the metabolic syndrome.<sup>16</sup> While this study showed us which elements of the metabolic syndrome were most predictive of cardiovascular mortality, it did not examine whether treatment of these risk factors improves outcomes. Therefore, we must integrate this knowledge with evidence from other important clinical trials in order to understand how best to treat our patients.

We will now explore the individual components of the metabolic syndrome as they relate to cardiovascular risk among older adults.

### Glycemic Control

According to the recently published Canadian Diabetes Association guidelines, the recommended glycemic target for persons with type 2 diabetes is an A1C of less than or equal to 7%.<sup>10</sup> The same glycemic target applies to otherwise healthy older adults. However, con-

sideration should be given to factors such as patient age, prognosis, and ability to perceive hypoglycemia. For older adults with multiple comorbidities, a high level of functional dependence, or limited life expectancy, a less stringent goal is often appropriate.<sup>10</sup>

When selecting any oral antihyperglycemic agent, one must consider the potential side effects. For example, the benefits of glycemic control must be weighed against the risk of hypoglycemia. Many risk factors for hypoglycemia are common among older adults, including adverse effects of medications, poor nutrition, cognitive impairment, autonomic dysfunction, and renal insufficiency.<sup>2</sup> Moreover, with aging, the mechanisms that regulate blood glucose become impaired, including a diminished glucagon response to hypoglycemia. Older adults tend to have more neuroglycopenic manifestations of hypoglycemia such as weakness, dizziness, and confusion, placing them at increased risk for traumatic falls with serious potential consequences.<sup>2,17</sup> Patients and their caregivers should be taught to recognize the signs and symptoms of hypoglycemia and mechanisms for prompt and effective treatment. They should also receive instruction on home blood-glucose monitoring. Agents that are known to cause hypoglycemia, such as the sulfonylureas, should be used with caution.<sup>10</sup>

Recently there has been controversy over the use of rosiglitazone due to the results of a meta-analysis that demonstrated an increase risk of myocardial infarction compared with other agents.<sup>18</sup> However, the results of this meta-analysis are controversial and their full consideration is beyond the scope of this article. A complete review of the pharmacologic agents available to treat diabetes and their use in older adults can be found in a previously published edition of this journal.<sup>19</sup>

During the United Kingdom Prospective Diabetes Study (UKPDS) of persons with type 2 diabetes, a reduction in median A1C from 8% to 7% was associated with a significant 25% reduction in

microvascular complications, but the 16% reduction in risk of myocardial infarction was not statistically significant.<sup>20</sup> The recently published long-term follow-up of this trial did show a significant reduction in myocardial infarction and total mortality in the intensively treated group that did not emerge until beyond completion of the intervention.<sup>21</sup> Moreover, the ACCORD and ADVANCE trials have called into question the value of tight glycemic control as it relates to vascular outcomes and mortality.<sup>22,23</sup> Taken together with UKPDS, the message is that one must intervene earlier and that it takes longer to see a glucose effect on cardiovascular disease compared to the effects of lipid or blood pressure lowering. Therefore, while glycemic control is clearly important in the management of diabetes, other cardiac risk factors, such as hypertension and hyperlipidemia, also play a significant role.

### Hypertension

Hypertension is a common comorbidity among persons with diabetes and its prevalence increases with advancing age.<sup>24</sup> In people with type 2 diabetes, hypertension is a major risk factor for cardiovascular disease.<sup>25,26</sup> The UKPDS blood-pressure trial demonstrated the benefits of more intensive blood pressure control in individuals with type 2 diabetes. Those persons randomized to tight blood pressure control (mean treated blood pressure 144/82 mmHg) with an angiotensin-converting enzyme (ACE) inhibitor or beta-blocker had a 24% relative risk reduction in diabetes-related end points, 32% fewer diabetes-related deaths, and 44% fewer strokes compared with those in the less-tight control arm (mean treated blood pressure 157/87 mmHg).<sup>27</sup>

Subsequent trials have demonstrated the macrovascular and microvascular benefits of lower blood pressure targets.<sup>28,29</sup> Currently, the recommended blood pressure for individuals with diabetes is less than or equal to 130/80 mmHg.<sup>10</sup> Consideration should be given to the use of an ACE inhibitor or angiotensin receptor blocker (ARB) as

**Table 1:** Defining the Metabolic Syndrome

National Cholesterol Education Program Adult Treatment Panel (NCEP/ATP III) <sup>12,15</sup>	International Diabetes Federation (IDF) <sup>15</sup>
<p><b>Any 3 of 5 traits</b></p> <p>Abdominal obesity (waist circumference men &gt;102 cm, women &gt;88 cm)</p> <p>Serum triglycerides &gt;1.69 mmol/L or drug treatment for elevated TG</p> <p>Serum HDL-C &lt;1 mmol/L in men, &lt;1.3 mmol/L in women or drug treatment for low HDL-C</p> <p>Blood pressure &gt;130/85 mmHg or drug treatment for elevated cholesterol</p> <p>Fasting plasma glucose &gt;6.1 mmol/L or drug treatment for elevated blood glucose</p>	<p>Increased waist circumference—different thresholds set for different race/ethnicity groups</p> <p><b>PLUS any 2 of:</b></p> <p>Triglycerides &gt;1.7 mmol/L or on treatment</p> <p>HDL &lt;1.03 mmol/L in men or &lt;1.29 mmol/L in women or treatment</p> <p>Systolic blood pressure &gt;130, diastolic blood pressure &gt;85 or treatment for hypertension</p> <p>Fasting plasma glucose (FPG) &gt;5.6 mmol/L or previously diagnosed type 2 diabetes: A oral glucose tolerance test recommended (but not required) for patients with an elevated FPG.</p>
<p>Source: Adapted from NCEP, 2000<sup>12</sup>; Alberti, et al., 2003<sup>14</sup>; Grundy, et al., 2005.<sup>15</sup></p>	

first-line antihypertensive therapy in individuals with diabetes.<sup>10</sup> However, several difference classes of antihypertensive agents have been shown to be effective for blood pressure lowering and cardiovascular risk reduction, and multiple agents are often required to achieve the recommended targets.<sup>30</sup>

The importance of treating hypertension in older adults is now well established.<sup>7,31,32</sup> Furthermore, treatment of hypertension in older adults with diabetes has been shown to reduce cardiovascular morbidity and mortality.<sup>33–35</sup> More recently, the Hypertension in the Very Elderly Trial (HYVET) looked at treatment of sustained hypertension (systolic blood pressure >160 mmHg) with indapamide, with or without perindopril, among persons 80 years of age or older, approximately 7% of whom had diabetes. Treatment was associated with a significant 34% reduction in cardiovascular events (death from cardiovascular causes or stroke, myocardial infarction or heart failure), driven mainly by a 64% reduction in fatal or nonfatal heart failure.<sup>7</sup> However, it is important to realize that the individuals included in HYVET were generally healthier than those in the broader older adult population and therefore the results may not apply to all

older persons. Specifically, patients with a clinical diagnosis of dementia and those requiring nursing care were excluded from participating and the baseline rates of known cardiovascular disease, diabetes, and heart failure were low. Moreover, in frail older adults with diabetes, avoidance of hypotension is an important concern due to the risk of falls, and may limit therapy. It is advisable to start with lower doses of medication and titrate based on blood pressure to minimize side effects.

### Dyslipidemia

The dyslipidemia classically associated with the metabolic syndrome or type 2 diabetes consists of high triglyceride levels, low HDL-cholesterol and small, atherogenic LDL particles.<sup>36</sup> Several trials have demonstrated the vascular benefits of aggressive LDL-lowering with statins for secondary prevention and primary prevention in high-risk, middle-aged people with diabetes.<sup>37–41</sup> Subgroup analyses of older cohorts in secondary prevention trials such as LIPID and CARE have shown the vascular benefits of statin therapy in older people with coronary heart disease, although they did not look specifically at those with diabetes.<sup>42,43</sup>

The PROSPER trial was designed to examine the safety and efficacy of statins for older adults.<sup>9</sup> The primary composite endpoint, defined as death from coronary heart disease, nonfatal myocardial infarction, fatal or nonfatal stroke was significantly reduced by 15% at 3 years among patients taking pravastatin compared with placebo. These results provide evidence that the benefits of statin therapy extend to people older than 70. This study showed benefit from lipid lowering over a relatively short time frame, which is particularly significant for older adults in whom life expectancy may be reduced. Pravastatin was generally well tolerated with few adverse events and minimal drug interactions.<sup>44</sup> While this trial supports the use of statins in older adults, we are not aware of any randomized controlled trials intentionally designed to address the issue of lipid-lowering therapy among older adults with diabetes. A post-hoc analysis of individuals age 65–75 years at randomization in CARDS, a primary prevention study of atorvastatin in people with diabetes, demonstrated substantial benefits of statin therapy in older adults with type 2 diabetes.<sup>45</sup>

The vast majority of older adults

with diabetes will be considered high risk for vascular events. Therefore, in accordance with the Canadian Diabetes Association Guidelines and the Canadian Dyslipidemia Guidelines, first-line therapy should be with a statin to achieve a target LDL-C of less than or equal to 2.0 mmol/L whenever possible.<sup>10</sup> Given concerns of potential drug interactions and altered metabolism related to aging, it is generally advisable to start with a low dose and titrate up slowly.<sup>46</sup> However, higher initial doses of statin may be indicated for people with recent myocardial infarction or stroke.<sup>47,48</sup> Furthermore, poor adherence to statin therapy is common among older adults; therefore, patient education and follow up is important.<sup>49</sup>

In addition to statin therapy, lifestyle modifications such as physical activity, a healthy diet, and weight loss for overweight individuals may improve lipid levels and have additional benefits in these patients.

### Lifestyle Interventions

The risk of developing type 2 diabetes increases with obesity, lack of physical activity, and loss of muscle mass, all of which may develop with aging.<sup>2</sup> Exercise is of benefit in improving insulin sensitivity and reducing cardiac risk in people with diabetes.<sup>50</sup> Weight loss can improve pancreatic endocrine function and insulin sensitivity in obese older adults.<sup>51</sup> Additional benefits of exercise for older adults include increased strength and balance,

reduced falls, decreased pain from osteoarthritis, improvement in depressive symptoms, and enhanced quality of life.<sup>52</sup> These can occur even over a relatively short time frame. Walking is often the most feasible and popular form of aerobic exercise for older adults.<sup>10</sup> In addition to general aerobic activities, resistance training can produce important therapeutic benefits and should also be encouraged.<sup>53</sup> Patients should be advised of the effects of exercise on blood sugar and strategies implemented to avoid hypoglycemia, such as consumption of extra carbohydrates or adjustment of medications. Assessment with an exercise stress test should be considered for patients with significant comorbidities prior to embarking on an exercise regimen. Referral to a specialized program, such as a cardiac rehabilitation center, can be an excellent resource.

Lifestyle modification is effective in the prevention of diabetes mellitus in those at high risk for the development of the disease. In the Diabetes Prevention Program trial, lifestyle changes, including modest weight reduction, a healthy low-fat, low-calorie diet and regular physical activity, reduced the incidence of type 2 diabetes by 58% in persons with impaired fasting glucose or impaired glucose tolerance.<sup>54</sup> This effect was even greater in the subgroup of individuals over 60 years of age and much more effective than treatment with metformin.

Although many older adults with

diabetes are obese, this is less common than in middle-aged people with diabetes.<sup>2</sup> Lean individuals who develop diabetes in old age typically have reduced insulin secretion in response to a glucose load with relatively less insulin resistance.<sup>2</sup> These persons may be underweight and undernourished. In this population, a less restricted diet can improve quality of life with minimal adverse effects on glycemic control. In these circumstances, referral to a dietician can be highly beneficial. Optimal care of patients with diabetes (Table 2) involves input from a multidisciplinary team of health care professionals, especially among older adults.

### Conclusion

Diabetes is a growing epidemic and, as our population continues to age, the associated complications will have an even greater impact on society. In particular, diabetes is a strong risk factor for cardiovascular disease, resulting in a significant burden of morbidity and mortality. Management of glycemic control, hypertension, and hyperlipidemia through lifestyle modification and medications can improve cardiovascular risk in patients with diabetes. Glycemic control also has important benefits in reducing the risk of microvascular complications.

When implementing these strategies among older adults, special consideration must be given to geriatric concerns, and the benefits of therapy must be weighed against the potential risks.

**Table 2:** ABCs of Diabetes Care

	How often	Suggested Target
<b>A is for A1C:</b> a measure of the average blood sugar control over the past 3 months	At least twice per year Up to every 3 months if titrating medications or not meeting glycemic goals	A1C: 7% or less (if safely achievable) *less stringent targets may be appropriate if history of severe hypoglycemia, multiple comorbidities or limited life expectancy
<b>B is for Blood Pressure</b>	Every visit	<b>Less than 130/80 mmHg</b>
<b>C is for Cholesterol:</b> Primary target is LDL-C (low density lipoprotein cholesterol)	At least once per year	<b>LDL-C &lt;2.0</b>

Source: adapted from Abbate S, 2003.<sup>55</sup>



## Key Points

Cardiovascular disease is the leading cause of death among older adults with diabetes.

Glycemic control is only one component of management for older adults with diabetes: a combination of behaviour modification and pharmacologic therapy is appropriate.

Treatment of hypertension in older adults with diabetes has been shown to reduce cardiovascular morbidity and mortality.

The vascular benefits of aggressive LDL-lowering with statins for secondary prevention and primary prevention in high-risk, middle-aged persons with diabetes has been demonstrated.

Modest weight reduction, a healthy low-fat, low-calorie diet, and regular activity may reduce the incidence of type 2 diabetes in persons with impaired fasting glucose or impaired glucose tolerance.

Hopefully, future advances in this field will improve prevention and treatment of diabetes and reduce the associated complications to enhance quality of life in patients of all ages.

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