

# Treatment of diabetic vasculopathy: an overview

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**Abstract:** Type 2 diabetes is a chronic, degenerative, and noncommunicable disease, and is associated with a high prevalence of cardiovascular morbidity and mortality. The complications of diabetic vasculopathy are commonly grouped into microvascular and macrovascular complications. In diabetes, macrovascular complications are the commonest cause of morbidity and mortality and are responsible for a high incidence of vascular diseases. The aim of this review is to provide an overview of current treatment modalities for diabetic vasculopathy and highlight the importance of effective control of blood glucose, blood lipids, and blood pressure, as well as reduction of blood hypercoagulability, in lowering the macrovascular complications of diabetic vasculopathy. A literature review was conducted to retrieve the relevant information using the PubMed, Science Direct, and Google Scholar databases, reports, and books. People with type 2 diabetes are at markedly increased risk for cardiovascular disease and mortality. The initiators of vasculopathy that ultimately develop into long-term diabetic complications can be avoided by a healthy lifestyle and pharmacological intervention. Clinical trials have shown that effective control of blood glucose, blood lipids, blood pressure, and blood hypercoagulability can reduce macrovascular complications in patients with type 2 diabetes. Type 2 diabetes is responsible for premature mortality, predominantly through atherosclerotic vascular disease. Lifestyle modification and pharmacotherapy should be used to prevent or delay development of type 2 diabetes, including adverse cardiovascular outcomes. A multidisciplinary approach involving patients, health professionals, and diabetic educators should be used to combat the type 2 diabetes epidemic and its associated cardiovascular complications.

**Keywords:** type 2 diabetes, diabetic vasculopathy, macrovasculopathy, cardiovascular disease

## Introduction

Type 2 diabetes is a chronic, degenerative and noncommunicable disease, and is associated with a high prevalence of cardiovascular morbidity and mortality. The estimated prevalence of type 2 diabetes for 2010 has risen to 285 million from 151 million in 2000, representing 6.6% of the world's adult population, and the total number of people with diabetes is projected to rise to 438 million in 2030.<sup>1</sup> It is estimated that up to 80% of the 200 million people with diabetes globally will die of cardiovascular disease.<sup>2</sup> Type 2 diabetes acts as an independent risk factor for several forms of cardiovascular disease, and people with type 2 diabetes are 2–4 times more likely to develop cardiovascular disease due to a variety of risk factors<sup>3</sup> (Table 1). Studies have demonstrated that newly diagnosed, never-treated individuals with type 2 diabetes and no traditional cardiovascular risk factors develop early preclinical manifestations

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**Table 1** Type 2 diabetes and cardiovascular disease

- Cardiovascular disease is a major complication and the leading cause of early death among people with T2DM; about 65% of people with T2DM die from heart disease and stroke<sup>11</sup>
- Adults with T2DM are 2–4 times more likely to have heart disease or suffer a stroke than people without T2DM<sup>11</sup>
- High blood glucose in adults with T2DM increases the risk of heart attack, stroke, angina, and coronary artery disease<sup>12</sup>
- People with T2DM also have high rates of elevated blood pressure, lipid problems, and obesity, which contribute to their high rates of cardiovascular disease<sup>13</sup>
- T2DM is considered to be one of the six major controllable risk factors for cardiovascular disease.<sup>12</sup>

**Abbreviation:** T2DM, type 2 diabetes mellitus.

of macrovascular disease,<sup>4</sup> and even normoglycemic and normotensive offspring of parents with type 2 diabetes<sup>5,6</sup> and impaired glucose tolerance<sup>6</sup> had early manifestations of preclinical vasculopathy and a potentially increased risk for development of macrovascular disease.<sup>6</sup> Type 2 diabetes and its complications have a significant economic impact on individuals, families, health systems, and countries.<sup>7</sup> People with type 2 diabetes who have complications cost health care systems 3.5 times more than people with no evidence of complications.<sup>8</sup> It has been found that at least 10% of the total health budget is spent on the management of type 2 diabetes and its complications.<sup>9,10</sup> According to World Health Organization estimates, China will lose \$558 billion in national income due to heart disease, stroke, and type 2 diabetes alone in the period 2006–2015.<sup>11</sup> The initiators of vasculopathy that ultimately develop into long-term diabetic complications can be controlled and avoided by a healthy lifestyle and pharmacological intervention. This review examines the cardiovascular risk factors for type 2 diabetes, treatment modalities (lifestyle and pharmacological interventions), complications of diabetic vasculopathy, and the effects of effective control of blood glucose, blood lipids, blood pressure, and hypercoagulability in reduction of the macrovascular complications of diabetic vasculopathy.

A systematic review was conducted using the PubMed, Science Direct, and Google Scholar databases to identify the published literature on diabetic vasculopathy. Relevant reports and books were also consulted to retrieve appropriate information. For the database search, the following keywords were used: “type 2 diabetes”, “diabetic vasculopathy”, “macrovascular complications”, “hyperglycemia”, “hypertension”, “dyslipidemia”, and “hypercoagulability”. The reference lists of the relevant papers were also screened, and only studies published in the English language were considered for review.

## Treatment modalities in diabetic vasculopathy

Type 2 diabetes is a complex metabolic disorder characterized by persistent hyperglycemia in association with other cardiovascular risk factors. Important cardiovascular risk factors for diabetic vasculopathy include hyperglycemia, hypertension, hypercoagulability, and dyslipidemia, ie, high serum total cholesterol, elevated triglycerides, increased low-density lipoprotein (LDL) cholesterol, and decreased high-density lipoprotein (HDL) cholesterol.

Diabetic patients require therapy for each of these metabolic abnormalities to reduce atherogenesis and prevent cardiovascular complications.<sup>14</sup> The main aims of treatment are to correct insulin resistance, beta cell dysfunction, and hepatic glucose output, as well as to prevent, delay, or reverse diabetic complications. The modalities of treatment currently available to manage type 2 diabetes include lifestyle modification (appropriate diet and exercise programs) and pharmacological intervention. Effective management of blood lipid, hypertension, blood glucose, and blood hypercoagulability can contribute to reduction of cardiovascular risk in people with type 2 diabetes.

## Lifestyle intervention

Lifestyle management is recognized as being an essential part of management of type 2 diabetes and prevention of cardiovascular disease. Dietary restriction is recommended in type 2 diabetes to achieve weight loss and reduce the risk factors for cardiovascular disease. Weight loss lowers blood pressure and improves blood lipid concentrations, especially triglycerides and very low-density lipoprotein cholesterol. Exercise improves glycemic control, reduces certain cardiovascular risk factors, and increases psychological well being.<sup>15</sup> Because obesity, hyperlipidemia, and hypertension are commonly associated with type 2 diabetes, treatment is frequently aimed at reversing all of these abnormalities by weight reduction via a combination of caloric restriction and increased energy expenditure through regular physical exercise. In addition, physical training in patients with type 2 diabetes has been shown to produce changes in insulin resistance, such as an increase in the number of skeletal muscle glucose transporters, which may reduce the need for hypoglycemic agents.<sup>16</sup>

## Pharmacotherapy

In the majority of patients, type 2 diabetes is not well controlled by lifestyle modification, so presents major challenges for pharmacotherapy.<sup>17</sup> The International

Diabetes Federation global guidelines for type 2 diabetes recommend a glycosylated hemoglobin (HbA1c) of 6.5% or lower to reduce the risk of complications.<sup>18</sup> However, it was suggested to move the target to 8% in diabetic elders to simplify the diabetic regimen and to reduce the potential adverse effects of polypharmacy.<sup>19</sup> An elevated HbA1c level is considered to be an independent risk factor for coronary heart disease in people with and without diabetes. Selvin et al<sup>20</sup> reported that a “high normal” HbA1c level predicts an elevated risk of coronary heart disease in persons without diabetes, and suggested an HbA1c  $\geq$  4.6% as a cut point for risk of future coronary heart disease events. Because these goals are rarely achieved through lifestyle modification alone, antidiabetic agents and other drugs are usually required to prevent complications related to diabetic vasculopathy.<sup>18</sup> The major metabolic abnormalities and treatment modalities of diabetic vasculopathy are shown in Table 2.

## Treating hyperglycemia

Patients with type 2 diabetes who are not successfully treated by diet are generally prescribed oral hypoglycemic drugs. These drugs help to promote a decrease in blood glucose, apparently by increasing the release of insulin from beta cells in the pancreas or by increasing the sensitivity of peripheral tissues to insulin,<sup>21–23</sup> so are only effective in patients with some capacity for endogenous insulin production. The main group of hypoglycemic agents includes biguanides, sulfonylureas, alpha-glucosidase inhibitors, meglitinides, thiazolidinediones, incretin mimetics, dipeptidyl peptidase-4 (DPP-4) inhibitors, and insulin.

Sulfonylureas work by stimulating insulin release from the pancreas and may slightly improve insulin resistance in peripheral target tissues. Sulfonylureas reduces HbA1c levels by 0.8%–2.0% and fasting plasma glucose concentrations by 3.3–3.9 mmol/L.<sup>24–26</sup> Nonsulfonylurea insulin secretagogue agents, eg, meglitinides (repaglinide, nateglinide), have a very short onset (15–30 minutes) of action and a short metabolic half-life (1–1.5 hours).<sup>27</sup>

Metformin is the most commonly used biguanide. It is suggested as the first-line drug of choice for the treatment of type 2 diabetes, particularly in overweight and obese people and those with normal kidney function.<sup>28</sup> The major action of metformin in patients with type 2 diabetes is to reduce hepatic glucose output, primarily by decreasing gluconeogenesis, and to a lesser extent, by enhancing insulin sensitivity in hepatic and peripheral tissues. In placebo-controlled trials, metformin reduced HbA1c levels by approximately 1.0%–2.0%.<sup>25,29,30</sup>

Other effects include a reduction in plasma triglyceride levels and LDL cholesterol levels.

The thiazolidinediones (eg, rosiglitazone and pioglitazone) work by enhancing insulin sensitivity in both muscle and adipose tissue, and to a lesser extent, by inhibiting hepatic glucose production. These agents achieve notable improvement in insulin resistance, particularly when used in combination with other antidiabetic drugs, but have no effect on insulin secretion. As a class, the thiazolidinediones have also been shown to alter the lipid profile in patients with type 2 diabetes. These drugs have potentially favorable effects on other components of the insulin resistance syndrome. As insulin sensitizers, they may modify cardiovascular risk factors and reduce cardiovascular mortality in type 2 diabetes and subjects with insulin resistance.<sup>31,32</sup> However, there is a growing recognition that edema and weight gain can occur in patients treated with rosiglitazone and pioglitazone. Because people with diabetes are at increased risk of cardiovascular disease and many have pre-existing heart disease, the edema and weight gain may lead to congestive heart failure.<sup>33</sup> A meta-analysis of 42 clinical trials concluded that rosiglitazone was associated with an increased risk of myocardial infarction and cardiovascular death compared with nonthiazolidinedione therapies,<sup>34</sup> whereas another review of 19 trials of pioglitazone demonstrated reduction in nonfatal acute myocardial infarction, stroke, and all-cause mortality.<sup>35</sup> These findings were also supported by a recent study in Medicare beneficiaries in the US, which found that rosiglitazone was associated with an increased risk of stroke, heart failure, and death when compared with pioglitazone.<sup>36</sup> However, the interim US Food and Drug Administration review of an ongoing epidemiological study warned that use of pioglitazone for more than one year may be associated with an increased risk of bladder cancer.<sup>37</sup>

Alpha-glucosidase inhibitors (ie, acarbose, miglitol, voglibose) delay the absorbance of carbohydrates in the gut by inhibiting the alpha-glucosidase enzyme found in the brush border cells that line the small intestine. These enzymes are essential for the release of glucose from more complex carbohydrates.<sup>38</sup> Because they inhibit the breakdown and subsequent absorption of carbohydrates (dextrins, maltose, sucrose and starch; no effect on glucose) from the gut following meals, the biggest impact of these drugs is on postprandial hyperglycemia. They have been associated with a reduction in HbA1c of 0.7%–1.0% and fasting plasma glucose levels by 1.9–2.2 mmol/L.<sup>24,25,39,40</sup>

A recent advance in the management of type 2 diabetes has been the development and clinical use of

**Table 2** Treatment modalities for diabetic vasculopathy

Hyperglycemia Insulin resistance	Biguanides	Increase liver and muscle insulin sensitivity; decreases hepatic glucose production	Temporary nausea, loss of appetite, diarrhea, increased abdominal gas, metallic taste
	Sulfonylureas	Insulin secretagogues, bind to sulfonylurea receptor 1, cause depolarization and calcium influx, initiate insulin secretion	Hypoglycemia, weight gain, skin reaction, dark urine, stomach upset, increased sensitivity to sun
	$\alpha$ -glucosidase inhibitors	Delay absorption of polysaccharides and act to attenuate postprandial glucose excursions	Slight weight gain, gastrointestinal disturbances, ie, abdominal bloating, flatulence, diarrhea
	Sulfonylurea-like agents	Insulin secretagogues, bind to sulfonylurea receptor 1 at a different site to sulfonylureas, resulting in rapid and shorter insulin response	Weight gain, hypoglycemia
	Thiazolidinediones	Insulin sensitizers that improve glucose uptake in adipose tissues and skeletal muscles	Fluid retention, decreased hemoglobin, congestive heart failure, fractures
	Glucagon-like peptide-1 mimetics	Bind to glucagon-like peptide-1 receptor, increase glucose-dependent insulin secretion and glucagon suppression	Gastrointestinal side effects, avoid in renal failure
	Dipeptidyl-peptidase-4 inhibitors	Prolong and enhance the activity of endogenous glucagon-like-peptide-1 and glucose-dependent insulinotropic polypeptide, serve as prandial stimulators of insulin secretion and regulate glycemia	Unconfirmed association with pancreatitis
Hypertension	Insulin	Reduces hepatic glucose output and increases peripheral glucose utilization	Hypoglycemia, weight gain, skin rashes, shortness of breath, swelling of face
	ACE inhibitors	Block formation of AT-II, increase bradykinin level; as a result, reduce vasoconstriction, reduce sodium and water retention, and increase vasodilation (through bradykinin)	Long-lasting dry cough, skin rash, swelling of your sinuses, sore throat, elevated blood potassium level, feeling sick or vomiting, indigestion, diarrhea, or constipation
	Angiotensin receptor blockers	Competitive inhibition of AT-II receptor (type 1); effect more specific on AT-II action, less or none on bradykinin production or metabolism	Hyperkalemia, dizziness, headache, drowsiness, diarrhea, metallic taste, rash
	Beta-blockers	Inhibit renin release and AT-II and aldosterone production and lower peripheral resistance; may decrease adrenergic outflow from the central nervous system	Dizziness, lightheadedness, drowsiness and blurred vision
	Calcium channel blockers	Dilate peripheral arterioles and thereby reduce BP by inhibiting calcium influx into arterial smooth muscle cells	Constipation, feeling sick, palpitations, tiredness, dizziness, and rashes
Dyslipidemia	Diuretics	Lower BP by depleting body sodium stores, resulting in reduction of total blood volume and cardiac output; initially peripheral vascular resistance increases but declines when cardiac output returns to normal level (6–8 weeks)	Increased urination, low sodium in your blood (hyponatremia), increased blood sugar, and increased cholesterol
	Statins	Increase lipid profile and decrease atherogenic tendency; lower LDL-C, improve TC to HDL-C ratio, lower apo B	Migraine headaches, pain and weakness of muscles, drowsiness, dizziness, constipation
	Fibric acid derivatives	Increase lipid profile and decrease atherogenic tendency; lower triglycerides, raise HDL-C, lower TC to HDL-C ratio and shift LDL from smaller to larger particles	Abdominal pain, constipation, diarrhoea, nausea, headache, fatigue, dizziness, muscle tenderness or soreness
Platelet activation and aggregation	Aspirin	Antiplatelet effect	Irritation of the stomach or bowel, indigestion, nausea, dizziness, ringing in the ears, vomiting
	Clopidogrel	Irreversible blockade of the adenosine diphosphate receptor on platelet cell membranes	Bleeding/bruising, stomach upset/pain, diarrhea/constipation
	Ticlopidine	Interferes with platelet membrane function	Allergic reaction, difficult breathing, swelling of face, lip, tongue/throat

**Abbreviations:** ACE, angiotensin-converting enzyme; BP, blood pressure; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; TC, total cholesterol; apo B, apolipoprotein B; AT-II, angiotensin II.

incretin-based therapies, ie, glucagon-like peptide-1 (GLP-1) receptor analogs (eg, exenatide) and DPP-4 inhibitors (eg, sitagliptin, vildagliptin, saxagliptin).<sup>41–44</sup> The former are given subcutaneously while the latter are taken orally. GLP-1 receptor agonists mimic the action of GLP-1 and increase the incretin effect in patients with type 2 diabetes, stimulating the release of insulin. These drugs help in preservation of beta cell mass and function, do not produce hypoglycemia, help in weight reduction, and are associated with significant reductions in HbA1c of 1%.<sup>41</sup> DPP-4 inhibitors prevent degradation of endogenous GLP-1 and glucose-dependent insulinotropic polypeptide, thereby helping in glycemic control, and are associated with reductions in HbA1c of 0.6%–0.7%, with no weight gain and a low risk of hypoglycemia.<sup>42</sup>

## Treating hypertension

The coexistence of hypertension in patients with type 2 diabetes is particularly destructive because of the strong linkage between both these two conditions and macrovascular complications.<sup>45</sup> Hypertension is present at the time of diagnosis of type 2 diabetes in over one-third of patients, often coexisting with dyslipidemia, central obesity, and increased susceptibility to cardiovascular disease.<sup>46</sup> The guidelines put out by the JNC7<sup>45</sup> and American Diabetes Association<sup>47</sup> recommend control of blood pressure in patients with type 2 diabetes to levels of 130/80 mmHg or lower. These guidelines also recommend lifestyle modifications, such as smoking cessation, avoidance of excess alcohol, and exercise. Studies of hypertension control in type 2 diabetes show that effective control of blood pressure leads to substantially reduced risk of cardiovascular events and death.<sup>48–52</sup>

Regarding the selection of medications, the evidence shows that diuretics, angiotensin-converting enzyme (ACE) inhibitors, beta-blockers, angiotensin II receptor blockers, and calcium antagonists have a benefit in the treatment of hypertension and that the majority of patients with type 2 diabetes require two or more drugs to achieve blood pressure control. Thiazide diuretics are found to be beneficial in type 2 diabetes, either alone or as part of a combined regimen.<sup>45</sup> ACE inhibitors reduce macrovascular complications in type 2 diabetes, appear to improve insulin sensitivity and glucose metabolism,<sup>31,53</sup> and can be used alone, but are found to be much more effective when combined with a thiazide diuretic or other antihypertensive drugs.<sup>45</sup> Beta-blockers, especially beta 1-selective agents, are beneficial in type 2 diabetes as part of multidrug therapy, but their value as monotherapy is less clear.<sup>45</sup> Angiotensin II receptor blockers

also show protective cardiovascular effects similar to those of ACE inhibitors, particularly in type 2 diabetic patients after myocardial infarction and in those with heart failure.<sup>54</sup> Although beta-blockers are indicated in type 2 diabetic patients with ischemic heart disease, they are found to be less effective than angiotensin II receptor blockers in preventing stroke.<sup>55</sup> Calcium antagonists may be useful to control blood pressure in type 2 diabetes, particularly as part of combination therapy.<sup>45</sup> Patients taking treatment for high blood pressure based on a calcium channel blocker have a lower risk of developing type 2 diabetes and associated complications than patients using a beta-blocker.<sup>56</sup>

## Treating dyslipidemia

Dyslipidemia is strongly correlated with insulin resistance and hyperinsulinemia.<sup>17</sup> It is present at the time of diagnosis as a part of the insulin resistance syndrome and persists despite treatment of glycemia. Lipid-lowering agents reduce the risk of major macrovascular events in patients with type 2 diabetes.<sup>57,58</sup> Statins (HMG-CoA reductase inhibitors) are considered to be first-line therapy for the majority of type 2 diabetic patients.<sup>17</sup> Treating dyslipidemia in type 2 diabetes with statins has demonstrated benefit in both the primary and secondary prevention of cardiovascular disease.<sup>57,59,60</sup> Several studies have also shown benefits associated with fibrate treatment.<sup>61–63</sup> Statins lower LDL-C, improve the total cholesterol to HDL-C ratio, and lower apolipoprotein B, while fibrates lower triglycerides, raise HDL-C, lower the total cholesterol to HDL-C ratio, and shift LDL from smaller to larger particles.<sup>31</sup> Recent evidence suggests that use of moderate to high doses of statins increases the risk of developing new-onset diabetes,<sup>64,65</sup> and it has been advised to exercise caution in using statins for patients with cardiovascular risk or where cardiovascular benefit has not been proven.<sup>64</sup>

## Treating hypercoagulability

Patients with type 2 diabetes have heightened platelet activity, which increases their risk of cardiovascular events.<sup>66</sup> Aspirin, clopidogrel, dipyridamole, and the glycoprotein IIb/IIIa receptor antagonists reduce cardiovascular risk in patients with type 2 diabetes<sup>17</sup> due to their antiplatelet effects. A considerable body of evidence has accumulated about the benefits of antiplatelet therapy, in most cases for aspirin, in patients with a previous cardiovascular event.<sup>17</sup> Aspirin irreversibly inhibits prostaglandin H synthase (cyclo-oxygenase-1) in platelets and megakaryocytes, and

thereby blocks the formation of thromboxane A<sub>2</sub>, a potent vasoconstrictor and platelet aggregant.<sup>67</sup> The thienopyridine derivatives (clopidogrel, ticlopidine) are metabolized in the liver to active compounds which covalently bind to the adenosine phosphate receptor on platelets and dramatically reduce platelet activation. Dipyridamole inhibits phosphodiesterase, which inactivates cyclic adenosine monophosphate. Increased intraplatelet concentrations of cyclic adenosine monophosphate reduce the activation of cytoplasmic second messengers. Dipyridamole also stimulates prostacyclin release and inhibits thromboxane A<sub>2</sub> formation. Glycoprotein IIb/IIIa receptor antagonists block the final common pathway for platelet aggregation.

## Clinical trials on prevention and treatment of diabetic vasculopathy

### Lifestyle intervention

Increased rates of obesity and decreased physical activity are strongly linked with an increased prevalence and incidence of type 2 diabetes.<sup>68</sup> Obesity is a predictor of both coronary heart disease and type 2 diabetes, and about 80%–90% of type 2 diabetes is attributable to excess weight.<sup>69</sup> Obesity adversely affects blood pressure and plasma lipid levels, and even moderate weight loss can improve glycemic control, insulin sensitivity, blood pressure, and lipid profiles in obese patients with type 2 diabetes, at least in the short term.<sup>69–73</sup> Diet can be used to achieve or maintain a healthy weight and to achieve target metabolic outcomes, including improved plasma glucose and lipid levels, as well as lowering of elevated blood pressure.<sup>73</sup> Patients with type 2 diabetes are encouraged to eat carbohydrates in the form of whole grains, fruit, vegetables, and low-fat dairy products, to use sweeteners in place of other carbohydrates in the diet, and to reduce intake of saturated fats.<sup>71</sup> Exercise directly improves insulin sensitivity, glycemic control, plasma lipid levels, blood pressure, and body weight, and decreases adverse cardiovascular events.<sup>74</sup> Exercise can also affect these factors indirectly by decreasing plasma insulin levels.<sup>75</sup> The majority of the studies focusing on diabetes prevention have not been long enough to assess cardiovascular outcomes.<sup>76</sup> Moreover, the original designs of these studies were not intended to examine cardiovascular outcomes, which restricted the statistical analysis to detecting reductions in the incidence of cardiovascular and mortality risk.<sup>76</sup> Because there are no complete studies assessing the effect of intensive lifestyle intervention on cardiovascular outcome in type 2 diabetes, further follow-up of ongoing trials is necessary to acquire evidence-based information.<sup>76</sup>

A multicenter, randomized controlled trial known as Look AHEAD (Action for Health in Diabetes) enrolled 5145 obese patients with type 2 diabetes for an estimated period of 10 years to evaluate if an average weight loss of 7% body weight by altered diet and exercise habit reduces the risk of cardiovascular disease.<sup>77</sup> The one-year results of Look AHEAD demonstrate that intensive lifestyle intervention results in clinically significant weight loss in people with type 2 diabetes which is associated with improved diabetes control and cardiovascular risk factors and, at the same time, reduced medication use and cost.<sup>78</sup> Several further years are needed to determine whether the initial weight loss can be maintained, whether intentional weight loss has a long-term effect on risk factors, and whether the weight loss reduces cardiovascular mortality and morbidity.<sup>78,79</sup> Li et al reported 20-year follow-up results on incidence of type 2 diabetes and cardiovascular disease from the China Da Qing Diabetes Prevention Study<sup>80</sup> and found that the reduction in diabetes incidence persists in the combined intervention group, which is also supported by the findings from the Finnish Diabetes Prevention Study<sup>81</sup> (with seven years of follow-up). However, whether lifestyle intervention also leads to reduced cardiovascular disease and mortality remains unclear.

A meta-analysis demonstrated that lifestyle intervention (diet and physical activity) led to a 63% reduction in the incidence of type 2 diabetes in high-risk groups.<sup>76</sup> This analysis included intensive lifestyle intervention studies<sup>82–87</sup> which showed that there were reductions in cardiovascular risk factors in patients with type 2 diabetes, impaired glucose tolerance, and impaired fasting glycemia, and in obese individuals with and without the metabolic syndrome. However, evidence for the effect of lifestyle intervention on clinical cardiovascular outcomes was lacking. Another review<sup>88</sup> conducted by Orozco et al, which included eight trials,<sup>83,86,87,89–93</sup> had an exercise plus diet arm (2241 participants) and a standard recommendation arm (2509 participants), with a study duration of 1–6 years. The analysis found that the incidence of type 2 diabetes was reduced by 37% (relative risk reduction) with exercise and diet, but no study reported relevant data on type 2 diabetes and cardiovascular disease-related morbidity, all-cause mortality, and quality of life. The investigators recommended that there is a need for studies to explore the effect of exercise and diet on quality of life, morbidity, and mortality, with a special focus on cardiovascular outcomes.

## Glycemia control

Prolonged hyperglycemia is now recognized as a major factor in the pathogenesis of diabetic vasculopathy.<sup>31</sup> Positive

correlations between measures of glycemic control and cardiovascular outcomes were also identified by several observational studies.<sup>94–96</sup> Results from clinical trials examining the effect of intensive glucose control on cardiovascular disease have failed to show consistent beneficial effects on cardiovascular events.<sup>97–100</sup> It was demonstrated that intensive glucose control reduces the risk of microvascular complications among patients with type 2 diabetes, but its effect on cardiovascular disease is uncertain.<sup>49,101,102</sup> Early data from UKPDS (the United Kingdom Prospective Diabetes Study) 34 suggested a protective effect of improved glucose control on cardiovascular disease, cardiovascular mortality, and all-cause mortality.<sup>97</sup> However, a number of large randomized, controlled trials<sup>98,100,103–105</sup> have reported conflicting results. In three published trials, ie, ADVANCE (Action in Diabetes and Vascular Disease: Preterax and Diamicon Modified Release Controlled Evaluation),<sup>98</sup> VADT (Veterans Affairs Diabetes Trial),<sup>103</sup> and NAVIGATOR (Nateglinide and Valsartan in Impaired Glucose Tolerance Outcomes Research),<sup>104</sup> no effect of intensive glucose control on major cardiovascular events was reported. However, ACCORD (Action to Control Cardiovascular Disease in Diabetes)<sup>100</sup> demonstrated an increased risk of death from cardiovascular causes and total mortality associated with intensive glucose control. In the PROactive (Prospective Pioglitazone Clinical Trial in Macrovascular Events) study,<sup>106</sup> patients treated with pioglitazone had a significant 16% reduction in mortality, nonfatal myocardial infarction, and stroke.

A meta-analysis, which enrolled 33,040 participants, measured the effect of intensive glucose-lowering treatment on cardiovascular outcomes and death in patients with type 2 diabetes,<sup>107</sup> and analyzed five randomized, controlled trials (ie, UKPDS,<sup>49,97</sup> ADVANCE,<sup>98</sup> VADT,<sup>103,108</sup> ACCORD,<sup>100</sup> and PROactive<sup>105–106,109</sup>). This review demonstrated that intensive glucose control has cardiovascular benefit compared with standard treatment for individuals with type 2 diabetes and a significant 17% reduction in nonfatal myocardial infarction events and a significant 15% reduction in coronary heart disease events.

Marso et al<sup>110</sup> performed a meta-analysis of six studies<sup>49,97,98,100,103,111</sup> (four randomized, controlled trials; 27,544 patients; mean follow-up 5.4 years; duration 1990–2009) evaluating the effect of intensive glucose control on major adverse cardiovascular events (ie, all-cause mortality, nonfatal myocardial infarction, and nonfatal stroke) in patients with type 2 diabetes. The review failed to establish any effect on mortality from cardiovascular or any cause or nonfatal stroke, but did find a significant

14% reduction in nonfatal myocardial infarction in patients randomized to intensive glucose control. Another systematic review<sup>112</sup> of five trials (1950–2009)<sup>49,97,98,100,103</sup> conducted by Kelly et al involving 27,802 adults found that intensive glucose control reduced the risk for some cardiovascular outcomes, but did not reduce the risk of cardiovascular death or all-cause mortality. Coutinho et al<sup>113</sup> conducted a meta-regression analysis of published data (1966–1996) from 20 studies<sup>114–134</sup> of 95,783 individuals followed for 12.4 years and demonstrated a progressive relationship between glucose levels and cardiovascular risk extending even below the diabetic threshold. A recent meta-analysis demonstrated a modest (9%) but statistically significant reduction in cardiovascular disease outcomes, including nonfatal myocardial infarction, and no increase in mortality.<sup>135</sup> In light of these study results, it is apparent that further research is needed to examine pharmacological approaches for the management of hyperglycemia which also affect cardiovascular disease risk reduction.

## Blood pressure control

Patients with type 2 diabetes and hypertension are always at increased risk of morbidity and mortality from cardiovascular events. Diabetic vasculopathy can be improved by lowering blood pressure with antihypertensive drugs which have antiatherogenic effects, eg, ACE inhibitors, angiotensin II receptor blockers, beta-blockers, and calcium channel blockers. Randomized controlled trials that have involved large numbers of hypertensive diabetic patients, eg, UKPDS 38,<sup>50</sup> the HOT (Hypertension Optimal Treatment) trial,<sup>48</sup> SHEP (the Systolic Hypertension in the Elderly Program),<sup>136–138</sup> the Syst-EUR (Systolic Hypertension in Europe) trial,<sup>137–139</sup> the HOPE (Heart Outcomes Prevention Evaluation), study<sup>140</sup> the LIFE (Losartan Intervention For Endpoint Reduction in Hypertension) study,<sup>141</sup> and ALLHAT (the Anti-hypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial),<sup>142</sup> have revealed that adequate blood pressure control improves cardiovascular outcomes, especially for stroke, when aggressive blood pressure targets are met.<sup>48,50,143,144</sup>

The UKPDS investigation of hypertension demonstrated that a 10 mmHg reduction in mean systolic blood pressure (SBP) led to a 44% reduction in stroke incidence, with more than 20% of patients requiring three or more drugs to achieve target blood pressure.<sup>50</sup> It was found that in the tight control group (150/85 mmHg), there were substantial reductions in risk for any type 2 diabetes endpoint, deaths related to type 2 diabetes, and stroke, but a nonsignificant change in all-cause mortality. In another landmark trial, ie, the HOT

study, patients with type 2 diabetes randomly assigned to a diastolic blood pressure (DBP) target of 80 mmHg had a significantly reduced risk of cardiovascular death and major cardiovascular events, and a nonsignificant trend toward improved overall mortality compared with those who had a target DBP of 90 mmHg.<sup>48</sup> The study supports a lower DBP target in order to reduce stroke events in patients with diabetes. In the Syst-EUR trial,<sup>51</sup> mean decreases in SBP (8.6 mmHg) and DBP (3.9 mmHg) in type 2 diabetic patients led to improvement in risk of cardiovascular death, all cardiovascular events, and stroke. In the ADVANCE study,<sup>98</sup> blood pressure was lowered to 135/78 mmHg with positive effects, but the ACCORD study<sup>100</sup> did not find any benefit from lowering blood pressure below 120/80 mmHg.

In the Micro-HOPE (Micro-Heart Outcomes Prevention Evaluation) study, the cardiovascular effects of ramipril (an ACE inhibitor) were evaluated in patients with type 2 diabetes.<sup>140,145</sup> The drug showed significantly lower risks for cardiovascular outcomes, total mortality, and microvascular diabetes complications. The Micro-HOPE study<sup>140</sup> showed that ramipril reduced the risks of stroke by 33% in patients with type 2 diabetes and this treatment was also associated with a significant 34% reduction in new diagnosis of type 2 diabetes cases. The evidence suggests that angiotensin II receptor blockers have cardiovascular protective effects similar to those of ACE inhibitors, particularly in post-myocardial infarction patients and in those with heart failure.<sup>54</sup> ONTARGET (Ongoing Telmisartan Alone and in Combination with Ramipril Global Endpoint trial) is the first trial to demonstrate that telmisartan (an angiotensin II receptor blocker) is as effective as ramipril for cardiovascular protection in a high-risk, ACE-tolerant population.<sup>146</sup>

Clinical trials have impressively shown that treatment with conventional antihypertensive agents, including cardioselective beta-blockers, reduces morbidity and mortality in patients with systolic and diastolic hypertension.<sup>147</sup> The subanalysis of the CAPPP (Captopril Prevention Project) hypertension study compared captopril (an ACE inhibitor) with conventional antihypertensive treatment based on beta-blockers and diuretics.<sup>148</sup> The prospective evaluation of this study demonstrated that captopril is superior to conventional therapy in preventing cardiovascular events in hypertensive type 2 diabetic patients, especially in those with metabolic decompensation. The UKPDS<sup>50</sup> in type 2 diabetes with hypertension showed first-line beta-blockade to be at least as effective as ACE inhibition in preventing all primary macrovascular endpoints. In the UKPDS, atenolol was found to be as effective as captopril in reducing cardiovascular

events and stroke, despite equivalent blood pressure, at baseline and after nine years of follow-up.<sup>50</sup> Conversely, the LIFE study comparing losartan and atenolol showed a 39% reduction in all-cause mortality in favor of losartan in a diabetic subgroup.<sup>55</sup> Stroke incidence in the ALLHAT study was 15% higher with lisinopril (an ACE inhibitor) than with a thiazide diuretic.<sup>142</sup> The substudy of ASCOT (Anglo-Scandinavian Cardiac Outcomes Trial) reported that calcium channel blockers and ACE inhibitors may prevent progression of atherosclerosis in diabetic patients better than beta-blocker-based and diuretic-based regimens.<sup>149</sup>

A comparative analysis<sup>150</sup> was performed using eight trials (n = 130,270; 1996–2007) to analyze the effects of beta-blockers on cardiovascular outcomes in type 2 diabetic patients with hypertension. Myocardial infarction, stroke, cardiovascular mortality, and total mortality were the outcomes analyzed. The analysis found that beta-blockers have an increased risk of cardiovascular mortality when compared with renin-angiotensin system blockers in type 2 diabetic patients with hypertension. However, beta-blockers do not carry an increased risk for myocardial infarction, stroke, cardiovascular mortality, and total mortality when compared with control antihypertensive therapy in type 2 diabetic patients with hypertension.

Grossman and Messerli<sup>151</sup> examined 14 studies<sup>48,51,52,55,142,148,152–161</sup> to assess the effects of calcium antagonists in hypertensive patients with type 2 diabetes. When compared with conventional therapy, it was found that calcium antagonists had similar effects on coronary heart disease and total mortality, but may have reduced the risk of stroke. The analysis concluded that calcium antagonists are safe and effective for reducing most types of cardiovascular morbidity and mortality in type 2 diabetic patients with hypertension, although their use is associated with a lesser reduction of risk of heart failure than other treatments for hypertension.

Another review<sup>162</sup> of hypertension control in type 2 diabetes showed a clear and consistent effect of improved blood pressure control, ie, a substantially reduced risk of cardiovascular events and death.<sup>48,50–52,163–165</sup> Treatment of hypertension in type 2 diabetic patients with a blood pressure goal of 135/80 mmHg demonstrated dramatic benefits. Thiazide diuretics, angiotensin II receptor blockers, and ACE inhibitors may be the best first-line treatments, although other agents are usually necessary, and goals may not be achieved even with three or four agents. It was also advised that aggressive blood pressure control may be the most important factor in preventing adverse outcomes in patients with type 2 diabetes.



## Maintaining normal lipid profiles

Dyslipidemia contributes substantially to cardiovascular complications in patients with type 2 diabetes. Diabetic dyslipidemia comprises elevated total cholesterol and LDL cholesterol, decreased HDL cholesterol, and high triglyceride levels.<sup>166,167</sup> Studies have shown that lowering LDL cholesterol reduces the risk of major vascular events in a wide range of high-risk participants, including type 2 diabetics.<sup>168</sup> Randomized clinical trials in type 2 diabetes have consistently shown that statins significantly reduce the risk of major primary and secondary cardiovascular disease endpoints. Clinical trials of fibrate therapy have shown mixed results. A meta-analysis of data from 10 controlled trials<sup>169–178</sup> in a range of people with cardiovascular risk factors, including type 2 diabetes, found that primary prevention with statins had similar relative effects on cardiovascular risk as secondary prevention.<sup>179</sup> Evidence has gradually accrued on the benefit of statins in preventing cardiovascular disease in patients with type 2 diabetes. A meta-analysis conducted by the CTT (Cholesterol Treatment Trialists) Collaboration<sup>180</sup> using 14 trials<sup>59,60,168,169,174–177,181–186</sup> showed that statin therapy reduced the five-year incidence of major vascular events by about 20% per mmol/L reduction in LDL cholesterol, with similar proportional reductions in major coronary events, stroke, and the need for coronary revascularization in type 2 diabetic patients. The meta-analysis also highlighted that the average risk of a major vascular event was about 2.9% per year in people with type 2 diabetes and no known vascular disease.

CARDS (the Collaborative Atorvastatin Diabetes Study) randomized 2338 patients with type 2 diabetes without high LDL cholesterol and demonstrated that atorvastatin significantly reduced the incidence of new stroke by 48%, independent of patient age, gender, baseline cholesterol, and blood pressure levels.<sup>169</sup> These findings were confirmed by a subanalysis of the LIPID (Long-term Intervention with Pravastatin in Ischemic Disease) trial,<sup>187</sup> which showed reductions in stroke of 39% and 42% in patients with type 2 diabetes and impaired glucose tolerance, respectively. In HPS (the Heart Protection Study), simvastatin reduced stroke by 25% in the subgroup of patients with type 2 diabetes.<sup>173</sup> The Scandinavian Simvastatin Survival Study showed that treatment with simvastatin reduced stroke in a diabetic cohort by 62% compared with 23% in subjects without diabetes.<sup>188</sup>

Subgroup analysis of the Helsinki Heart Study, a five-year ischemic heart disease primary prevention trial using gemfibrozil, provided evidence for the potential benefit of

lipid-lowering agents in both nondiabetic and type 2 diabetic patients.<sup>189</sup> The subgroup analysis of VA-HIT (Veterans Affairs High-density lipoprotein Intervention Trial)<sup>190,191</sup> showed that gemfibrozil reduced coronary heart disease by 39% in type 2 diabetic patients, but the FIELD (Fenofibrate Intervention and Event Lowering in Diabetes) study<sup>192</sup> failed to show similar benefits. Post hoc analysis of the FIELD study suggested a benefit for type 2 diabetic patients with marked dyslipidemia.<sup>193</sup> Recently, the lipid arm of the ACCORD study examined whether combination therapy with a statin and fibrate would be beneficial in reducing cardiovascular disease in type 2 diabetes. The investigation failed to support the routine use of combination therapy with fenofibrate and simvastatin to reduce cardiovascular risk in the majority of high-risk patients with type 2 diabetes as compared with simvastatin alone.<sup>194</sup>

## Antiplatelet therapy

Atherosclerosis and vascular thrombosis are major contributors to diabetic vasculopathy, and it is generally accepted that platelets play a significant role in increasing the risk of cardiovascular disease.<sup>31</sup> Currently, aspirin is at the center of this research and is widely recommended for primary prevention of cardiovascular events in type 2 diabetic patients.<sup>195</sup> Aspirin reduces the risk of serious vascular events in patients at high risk by about 25% and also helps prevent the recurrence of such events as heart attack, hospitalization for recurrent angina, and recurrent strokes. Almost all of the major guidelines recommend aspirin for primary prevention of cardiovascular events in people with type 2 diabetes, based on the evidence extrapolated from trials of high-risk patients.<sup>196,197</sup> However, the POPA-DAD (Prevention of Progression of Arterial Disease and Diabetes) trial<sup>198</sup> demonstrated that aspirin did not prevent a first cardiovascular event or death in type 2 diabetic patients, which contradicts the recommendations made in many guidelines. It recommended that aspirin should be continued for secondary prevention of cardiovascular disease in patients with type 2 diabetes. The JPAD (Japanese Primary Prevention of Atherosclerosis with Aspirin for Diabetes) trial examined the efficacy of low-dose aspirin for the primary prevention of atherosclerotic events in type 2 diabetic patients and concluded that low-dose aspirin as primary prevention did not reduce the risk of cardiovascular events.<sup>199</sup>

A recent meta-analysis<sup>200</sup> using six trials<sup>198,199,201–204</sup> (10,117 patients, duration 1966–2008) also could not recommend use of aspirin for primary prevention of cardiovascular events in all patients with type 2 diabetes, and

suggested waiting for additional evidence from ongoing trials. This analysis suggested that the benefit of aspirin in primary prevention of major cardiovascular events or death in type 2 diabetic patients may be lower than in other high-risk populations. Aspirin significantly reduced the risk of myocardial infarction in men by 43%, whereas no benefit was found in women. Therefore, a clear benefit of aspirin in the primary prevention of major cardiovascular events in type 2 diabetic patients remains unproven and requires evidence from further studies.

Other antiplatelet drugs were also found to reduce the risk of cardiovascular events in type 2 diabetic patients. In a subgroup analysis of the CAPRIE (Clopidogrel versus Aspirin in Patients at Risk of Ischaemic Events) study, patients with type 2 diabetes taking clopidogrel seem to derive enhanced benefit from clopidogrel compared with aspirin.<sup>205,206</sup> A meta-analysis of six randomized trials<sup>207–212</sup> of GP IIb/IIIa inhibitors in type 2 diabetic patients with acute coronary syndrome showed that these drugs may significantly reduce mortality at 30 days, and recommended serious consideration of these agents in type 2 diabetic patients with acute coronary syndrome.<sup>213</sup> The subgroup analysis of 362 diabetic patients in the PRISM-PLUS (Platelet Inhibition in Ischemic Syndrome Management in Patients Limited by Unstable Signs and Symptoms) trial showed that triple therapy (aspirin, heparin, tirofiban) significantly reduced the incidence of myocardial infarction or death as compared with aspirin plus heparin.<sup>214</sup>

## Conclusion

Type 2 diabetes is a global epidemic with a devastating human, social, and economic impact. The costs of diabetes are enormous, both for health care services and through loss of productivity. The disease is responsible for premature mortality, predominantly through atherosclerotic vascular disease, either macrovascular or microvascular. However, macrovascular complications are more common, and most diabetic patients develop or die of macrovascular disease. Lifestyle modification and pharmacotherapy (tight blood pressure, and lipid and glycemic control) can prevent or delay the development of type 2 diabetes, including cardiovascular outcomes.

Studies have demonstrated that lifestyle interventions reduce cardiovascular risk factors, but evidence for long-term cardiovascular outcomes is lacking. Similarly, intensive glucose control in type 2 diabetic patients also failed to show consistent beneficial effects on cardiovascular events. On the contrary, the evidence shows that diabetic vasculopathy can be improved by lowering blood pressure using

antihypertensive drugs, maintaining normal lipid profiles with lipid-lowering agents, and minimizing atherosclerosis and vascular thrombosis with antiplatelet therapy. Above all, patient education and preventive care should be considered as an important way to combat the type 2 diabetes epidemic and its associated cardiovascular complications. A multidisciplinary approach involving patients, health professionals, and diabetic educators is the best strategy by which to bring “radical change” in understanding type 2 diabetes and improving quality of life.

## Disclosure

The authors report no conflict of interest in this work.

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