

# Type 2 diabetes: postprandial hyperglycemia and increased cardiovascular risk

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**Abstract:** Hyperglycemia is a major risk factor for both the microvascular and macrovascular complications in patients with type 2 diabetes. This review summarizes the cardiovascular results of large outcomes trials in diabetes and presents new evidence on the role of hyperglycemia, with particular emphasis on postprandial hyperglycemia, in adverse cardiovascular outcomes in patients with type 2 diabetes. Treatment options, including the new dipeptidyl peptidase-4 inhibitors and glucagon-like peptide-1 mimetics that primarily target postprandial hyperglycemia, are also discussed. Hyperglycemia increases cardiovascular mortality, and reducing hyperglycemia lowers cardiovascular risk parameters. Control of both fasting and postprandial hyperglycemia is necessary to achieve optimal glycosylated hemoglobin control. Therefore, anti-hyperglycemic agents that preferentially target postprandial hyperglycemia, along with those that preferentially target fasting hyperglycemia, are strongly suggested to optimize individual diabetes treatment strategies and reduce complications.

**Keywords:** postprandial hyperglycemia, diabetes mellitus, drugs, cardiovascular risk

## Introduction

Several landmark clinical trials have convincingly demonstrated that hyperglycemia is associated with the microvascular complications of diabetes.<sup>1-3</sup> These trials, along with epidemiological evidence, have provided the basis for treatment targets and algorithms recommended by the American Diabetes Association (ADA), the American Association of Clinical Endocrinologists (AACE), and the European Association for the Study of Diabetes (EASD).<sup>4-6</sup> Adequacy of glycemic control is almost universally assessed by glycosylated hemoglobin (HbA<sub>1c</sub>) – a measure of hemoglobin glycation over the erythrocyte life span that is proportional to the mean plasma glucose level over the preceding 2 to 3 months. An HbA<sub>1c</sub> <7% is recommended by the ADA/EASD and ≤6.5% by the AACE.<sup>4-6</sup> The mean value for individuals with normal glucose tolerance is 5.0% (upper limit of normal is 6.0%). HbA<sub>1c</sub> can be communicated with patients using estimated average glucose (eAG; HbA<sub>1c</sub> 5% = eAG 5.4 mmol/L, 97 mg/dL), so that they better understand how their blood glucose monitor readings are related to HbA<sub>1c</sub>.<sup>4</sup>

In addition to HbA<sub>1c</sub>, patients and physicians usually monitor and treat fasting plasma glucose (FPG) levels, but ignore or de-emphasize postprandial glucose (PPG) levels. There is no evidence that fasting hyperglycemia is more deleterious than postprandial hyperglycemia. Recent evidence, however, strongly suggests that control of postprandial hyperglycemia may be necessary to achieve HbA<sub>1c</sub> targets <7%.<sup>7</sup> Considerable data have accumulated indicating that elevated PPG levels, even in the absence of fasting hyperglycemia, increase the risk for cardiovascular (CV) disease (CVD). This article

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discusses and updates epidemiological and experimental studies linking postprandial hyperglycemia to CVD, and therapeutic approaches, both available and in development.

## Hyperglycemia and CVD

In people with type 2 diabetes, macrovascular disease, in particular CVD, is the major source of morbidity and mortality. The pathogenesis of CVD is complex and multifactorial. Smoking, obesity, dyslipidemia, and hypertension were considered the major “traditional” risk factors. Now diabetes itself is considered an important independent risk factor.<sup>8</sup> Having diabetes increases the risk for CVD mortality more than two-fold.<sup>9</sup> For example, in the INTERHEART study, a case-control study that assessed risk factors of coronary artery disease (CAD) worldwide in nearly 30,000 subjects, diabetes increased the odds ratio of having an acute myocardial infarction (MI) to 4.26 (99% confidence interval [CI], 3.51 to 5.18) in women and to 2.67 (99% CI, 2.36 to 3.02) in men (Table 1), making diabetes as important a risk factor as smoking, hypertension, obesity, and dyslipidemia.<sup>10</sup>

Numerous epidemiological studies have demonstrated a correlation between risk for CVD and plasma glucose levels (both fasting and postprandial) or HbA<sub>1c</sub> values.<sup>11</sup> The relationship between PPG and CV events persists even in the context of HbA<sub>1c</sub> levels in the nondiabetic range.<sup>11,12</sup> Moreover, the Funagata Diabetes Study showed that the cumulative survival rates from CVD of impaired glucose tolerance (IGT) and diabetes were reduced comparably, whereas the cumulative survival rate from CVD of impaired fasting glucose (IFG)

was not.<sup>13</sup> This suggests that IGT (or postprandial glycemia) is a more important CVD risk factor than IFG.

Epidemiological data suggest a strong link between CV risk and glucose control, but by nature of study design, cannot determine causality. Controlled clinical trials can determine causality and have examined the effects of glycemic control on vascular complications. The United Kingdom Prospective Diabetes Study (UKPDS),<sup>1</sup> the Diabetes Control and Complications Trial (DCCT),<sup>3</sup> the Action to Control Cardiovascular Risk in Diabetes (ACCORD),<sup>14</sup> and the Action in Diabetes and Vascular Disease: Preterax and Diamicon Modified Release Controlled Evaluation (ADVANCE)<sup>2</sup> were landmark controlled clinical trials that evaluated the benefits of intensive glucose control on diabetes complications. The UKPDS demonstrated a 25% risk reduction for microvascular complications ( $P = 0.0099$ ) and a 16% risk reduction for MI ( $P = 0.052$ ) in intensively treated patients.<sup>1</sup> Moreover, during a 10-year poststudy monitoring period, the UKPDS follow-up data demonstrated a persistent 15% risk reduction for MI ( $P = 0.01$ ) and a 13% risk reduction for all-cause mortality ( $P = 0.007$ ; Figure 1) despite a convergence in glycemic control levels between treatment groups.<sup>15</sup>

The DCCT follow-up study yielded a similar finding. The DCCT consisted of 1441 patients with type 1 diabetes randomized to intensive or conventional therapy for a mean of 6.5 years – 1983 through 1993.<sup>3,16</sup> Ninety-three percent of patients from the DCCT were followed until February 1, 2005, (mean 17-year follow-up) in the observational Epidemiology of Diabetes Interventions and Complications (EDIC) study. Intensive treatment reduced the risk of any CVD event by 42% (95% CI, 9% to 63%;  $P = 0.02$ ) and the risk of nonfatal MI, stroke, or death from CVD by 57% (95% CI, 12% to 79%;  $P = 0.02$ ).

The ACCORD<sup>14</sup> and ADVANCE<sup>2</sup> trials evaluated intensive blood glucose control below the current recommended levels of HbA<sub>1c</sub> and its impact on CV events. The ACCORD study consisted of 10,251 patients with type 2 diabetes with a median baseline HbA<sub>1c</sub> of 8.1% who were given intensive therapy to target HbA<sub>1c</sub> below 6% versus standard therapy (HbA<sub>1c</sub> = 7.0% to 7.9%). Thirty-five percent of patients had history of a previous CV event. The intensively treated arm of the study was terminated early because of higher mortality of 257 patients in this treatment group versus 203 patients in the standard therapy group. However, nonfatal MI occurred less often in the intensive group than in the standard group ( $P = 0.004$ ). Although overall difference in macrovascular events in ACCORD was not statistically significant between intensive and standard therapy, patients in the intensive

**Table 1** Association of risk factors with acute myocardial infarction in men and women

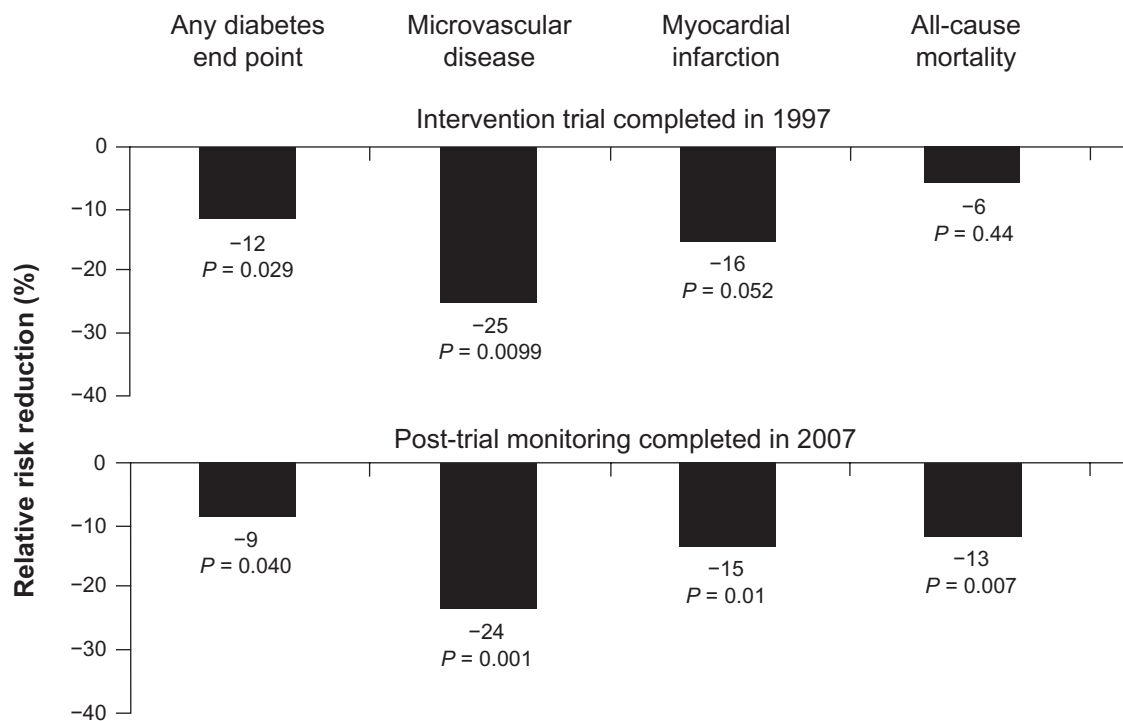
Risk factor	Sex	Odds ratio (99% CI) <sup>a</sup>
Diabetes	F	4.26 (3.51–5.18)
	M	2.67 (2.36–3.02)
Hypertension	F	2.95 (2.57–3.39)
	M	2.32 (2.12–2.53)
Current smoking	F	2.86 (2.36–3.48)
	M	3.05 (2.78–3.33)
Abdominal obesity	F	2.26 (1.90–2.68)
	M	2.24 (2.03–2.47)
ApoB/ApoA1 ratio <sup>b</sup>	F	4.42 (3.43–5.70)
	M	3.76 (3.23–4.38)

<sup>a</sup>Adjusted for age, sex, and geographic area.

<sup>b</sup>ApoB/ApoA1 ratio as an index of dyslipidemia.

Adapted from *The Lancet*, 364, Yusuf S, Hawken S, Öunpuu S, et al; for the INTERHEART Study Investigators. Effect of potentially modifiable risk factors associated with myocardial infarction in 52 countries (the INTERHEART study): case-control study, 937–952.<sup>10</sup> Copyright © (2004), with permission from Elsevier.

**Abbreviations:** F, female; M, male.



**Figure 1** Significant relative risk reduction in microvascular disease and any diabetes end point continued during 10 years of post-trial follow-up. Significant emergent risk reductions in myocardial infarction and all-cause mortality were observed only with extended follow-up.<sup>1,15</sup>

Adapted from *The Lancet*, 352, UK Prospective Diabetes Study (UKPDS) Group, Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33), 837–853.<sup>1</sup> Copyright © (1998), with permission from Elsevier.

therapy arm with no history of prior CV events or whose baseline HbA<sub>1c</sub> level was ≤8% had significantly fewer fatal or nonfatal CV events than the standard therapy arm. In these subgroups, intensive lowering of HbA<sub>1c</sub> was beneficial.<sup>14</sup>

The ADVANCE trial<sup>2</sup> studied 11,140 patients with type 2 diabetes randomized to receive standard therapy or gliclazide plus other medications to achieve HbA<sub>1c</sub> of ≤6.5% in the intensive control arm. With a median 5-year follow-up, mean HbA<sub>1c</sub> was lower in the intensive control group (6.5%) than in the standard control group (7.3%). Intensive control reduced the incidence of combined major macro- and microvascular events (18.1% versus 20.0% with standard control; hazard ratio [HR], 0.90; 95% CI, 0.82 to 0.98; P=0.01), as well as that of major microvascular events (9.4% versus 10.9%; HR, 0.86; 95% CI, 0.77 to 0.97; P=0.01), primarily because of a reduction in the incidence of nephropathy (4.1% versus 5.2%; HR, 0.79; 95% CI, 0.66 to 0.93; P=0.006). The ADVANCE trial, while positive for microvascular complications, had an event rate too low to have the statistical power to show a benefit of intensive glucose control on macrovascular complications.

The Veterans Affairs Diabetes Trial (VADT)<sup>17</sup> randomized 1791 patients with type 2 diabetes who had suboptimal control on oral medications or insulin with a median HbA<sub>1c</sub> of 8.4% for intensive glucose control or standard therapy, with a

goal of an absolute reduction of 1.5% HbA<sub>1c</sub> in the intensive versus standard therapy group. A major CV event, the primary outcome, occurred in 264 patients in the standard therapy group and 235 patients in the intensive therapy group (HR in the intensive therapy group, 0.88; 95% CI, 0.74 to 1.05; P=0.14). The incidence of primary outcome was not significantly lower in the intensive arm, but a subgroup analysis indicated that patients who had diabetes less than ~12 years derived CV benefit from intensive glycemic control.<sup>18</sup> Also, an embedded ancillary study within the main VADT showed that patients with previous history of increased baseline coronary or aortic calcium scores benefited less compared with patients who had low calcium scores.<sup>18</sup>

Together, the ACCORD,<sup>14</sup> ADVANCE,<sup>2</sup> and VADT<sup>17</sup> studies showed significant CV benefit in patients who had lower baseline HbA<sub>1c</sub>, no prior history of CAD, and shorter history of diabetes. Both the DCCT and UKPDS primary intervention studies also demonstrated long-term macrovascular benefits (>10 year follow-up).<sup>15,16</sup> Taken together, these studies illustrate that intensive glycemic control early in the course of diabetes is important in achieving CV benefit and provides guidance in terms of stratification of patients' target glycemic control. Thus, achieving a goal of HbA<sub>1c</sub> <7% is recommended, but a less intense target should be planned for

patients with history of severe CVD, severe hypoglycemia, or advanced microvascular or macrovascular disease complications. In addition to addressing diabetes control, physicians must optimize other modifying factors of CVD, including blood pressure, hyperlipidemia, obesity, smoking cessation, regular exercise, and healthy diet.<sup>18</sup> In the future, development of a risk profile and stratification will be important in customizing and guiding each patient's glycemic target and optimizing the benefits of intensive glucose control.

## Mechanisms of hyperglycemia-induced CV damage

Acute hyperglycemia has been linked to endothelial dysfunction. Monnier et al<sup>19</sup> reported that the urinary excretion rate of 8-iso-prostaglandin F<sub>2α</sub>, a marker of oxidative stress, correlated best with the glycemic variability assessed from the mean amplitude of glycemic excursions. To add another level of complexity, Ceriello et al<sup>20</sup> showed that not only was hyperglycemia associated with endothelial dysfunction in patients with and without type 2 diabetes, but also that oscillating glucose levels in 6-hour increments led to even greater dysfunction over time. Other studies also provided evidence that postprandial fluctuations, in addition to absolute increases in glycemia, contribute to oxidative stress and endothelial dysfunction.<sup>21–23</sup> Endothelial dysfunction seems to be affected via the vascular glycocalyx (an extracellular matrix of endothelial cell-derived proteoglycans, glycoproteins, and absorbed plasma proteins that act as a mechanosensor/mechanotransducer of blood flow and vascular shear stress) in a predominantly nitric oxide-dependent manner that promotes endothelial response to stimuli.<sup>24–26</sup> Nieuwdorp et al<sup>26</sup> utilized several techniques (eg, hyperglycemic clamp, flow-mediated dilation, glycocalyx tracers, and laboratory analytical tests) to assess endothelial function and coagulation parameters after hyperglycemic challenge in 10 healthy males. After glucose infusion, glycocalyx volume was decreased, mechanotransduction of flow-dependent arterial dilation was attenuated, and levels of prothrombin activation fragment F1 + 2, a factor that initiates coagulation cascades, were increased during hyperglycemia. Moreover, reducing PPG has been reported to improve endothelial dysfunction.<sup>23</sup> Oxidative stress caused by acute PPG spikes can contribute to macrovascular damage through oxidation of low-density lipoprotein, exacerbation of endothelial dysfunction, and other proatherogenic mechanisms. An overview of the complex interaction between factors that contribute to macrovascular complications of diabetes is presented in Figure 2.<sup>11,27</sup>

## Management of postprandial hyperglycemia

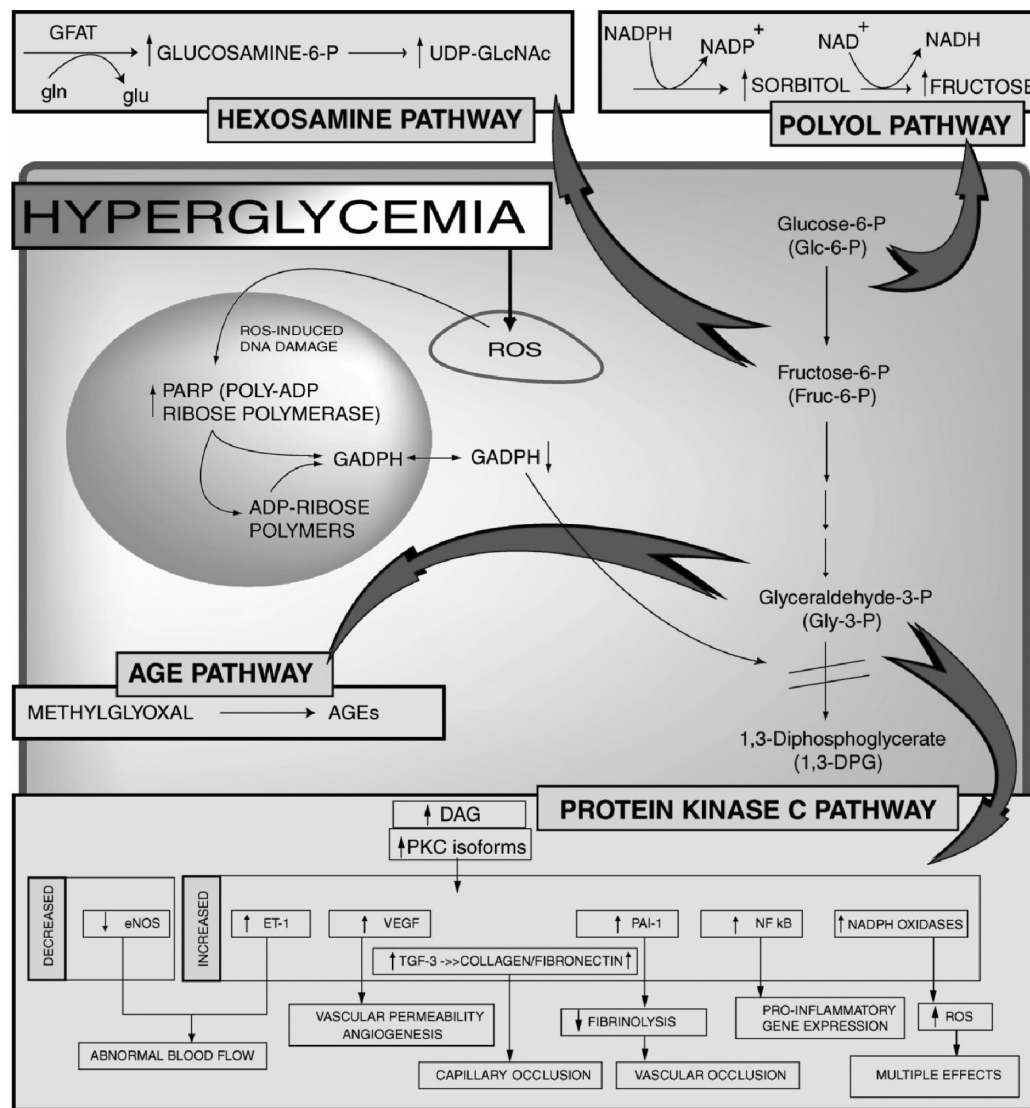
Postprandial glucose control is the rate-limiting step when optimizing blood glucose levels, as demonstrated in the study by Woerle et al.<sup>7</sup> This prospective interventional trial assessed the relative contributions of FPG and PPG in achieving recommended HbA<sub>1c</sub> goals. There were 164 patients with type 2 diabetes with HbA<sub>1c</sub> levels >7.5% (mean 8.7% ± 0.1) with target reductions of FPG to ≤5.6 mmol/L (≤100 mg/dL) and PPG at 90 minutes to ≤7.8 mmol/L (≤140 mg/dL). The study showed that when FPG (but not PPG) was at target, only 64% of patients achieved HbA<sub>1c</sub> ≤7%, whereas when both FPG and PPG were at target, 94% achieved HbA<sub>1c</sub> ≤7%. FPG values did not differ in patients with HbA<sub>1c</sub> above or below 7%. PPG accounted for ~90% of HbA<sub>1c</sub> values when HbA<sub>1c</sub> was <6.2%, but only ~40% when HbA<sub>1c</sub> was >8.9%.<sup>7</sup> These results further illustrate the importance of PPG in achieving better control of diabetes, consistent with an earlier study conducted by Monnier et al.<sup>28</sup> Most recently, results from the 4-T trial (Treating to Target in Type 2 Diabetes) indicated preprandial treatment with a rapid-acting insulin analogue resulting in significant decreases in PPG (−85 ± 59 mg/dL) compared with basal and biphasic insulin regimens (−61 ± 58 mg/dL and −67 ± 50 mg/dL, respectively).<sup>29</sup> However, while preprandial treatment with a rapid-acting insulin analogue resulted in significant reductions in HbA<sub>1c</sub> from baseline (−1.4% ± 0.1), comparisons with basal and biphasic insulin regimens were not significantly different (−1.3% ± 0.1 and −1.2% ± 0.1, respectively). It is interesting to note that no differences were found in FPG levels among the treatment groups.<sup>29</sup>

Furthermore, randomized controlled trials with agents that primarily target postprandial hyperglycemia have demonstrated CV benefit. The Study to Prevent Non-Insulin-Dependent Diabetes Mellitus (STOP-NIDDM) Trial showed that treating postprandial hyperglycemia with acarbose in patients with IGT reduced CV events.<sup>30</sup> PPG levels seen in diabetic patients correlate with carotid intima-media thickness (CIMT),<sup>31</sup> and treatment with antihyperglycemic agents such as nateglinide and acarbose – which target postprandial glycemia – reduces progression of CIMT.<sup>32,33</sup> In addition, optimal control of postprandial hyperglycemia has been associated with improved coronary blood flow<sup>34</sup> as well as possible reversal of myocardial perfusion abnormalities.<sup>35</sup>

## ADA, IDF, and AACE recommendations

The ADA in its *Standards of Medical Care in Diabetes—2009*<sup>4</sup> acknowledges that elevated PPG values are associated with increased CV risk – independent of FPG – and that the relative





**Figure 2** Mechanisms by which hyperglycemia induces mitochondrial overproduction of superoxide and activates 4 major pathways of hyperglycemic damage.<sup>11,27</sup> Copyright © 2005 American Diabetes Association from *Diabetes*. 2005;54:1615–1625.<sup>27</sup> Adapted with permission from the American Diabetes Association.

contribution of postprandial hyperglycemia to HbA<sub>1c</sub> is greater at HbA<sub>1c</sub> levels that are closer to 7%. The ADA recommends that individuals who have preprandial glucose values within target, but have HbA<sub>1c</sub> values above target, should monitor PPG 1 to 2 hours after the start of a meal. Treatment aimed at reducing PPG values to <10 mmol/L (<180 mg/dL) will likely lower HbA<sub>1c</sub> and may improve outcomes.<sup>4</sup>

The International Diabetes Federation (IDF) recommends that patients with diabetes manage their HbA<sub>1c</sub> levels to be <6.5% by addressing both FPG and PPG. The guidelines recommend that PPG levels not exceed 7.8 mmol/L (140 mg/dL) during the 2 hours postmeal. The frequency of self-monitoring to track PPG levels should be planned on an individual basis.<sup>36</sup> AACE guidelines are similar to those of the IDF, suggesting HbA<sub>1c</sub> ≤6.5%, FPG

<6 mmol/L (<110 mg/dL), and 2-hour PPG <7.8 mmol/L (<140 mg/dL).<sup>5</sup>

## Treatment considerations

### Nonpharmacologic interventions

Lifestyle management, including medical nutrition therapy (well-balanced diet), physical activity, and weight control, is recommended for all patients with type 2 diabetes. Decreases in HbA<sub>1c</sub> of approximately 1% to 2% have been demonstrated in randomized controlled clinical trials and observational studies evaluating medical nutrition therapy.<sup>37</sup> Of note, a recent systematic review and analysis by Boling et al<sup>38</sup> echoed previous suggestions that low-carbohydrate (ie, ≤40% energy from carbohydrates), rather than “well-balanced,” diets lead to better glycemic control (HbA<sub>1c</sub> decreases of -0.9%

to  $-1.5\%$ ) and may be the most efficacious dietary strategy for reducing obesity-related metabolic disease complications. Similarly, a meta-analysis by Barclay et al<sup>39</sup> indicated that low glycemic index and glycemic load diets result in reduced risk for type 2 diabetes and heart disease. The most recent and notable example of the advantages of weight loss, conferred by increased physical activity and low-calorie/low-fat diets,<sup>40</sup> are results from the 10-year follow-up of the Diabetes Prevention Program (DPP) Outcomes Study.<sup>41</sup> This follow-up, prospective analysis included 2766 patients at high risk for developing type 2 diabetes from the initial DPP trial who received standard medical information regarding health risks and type 2 diabetes and placebo, metformin, or intensive lifestyle intervention (for details, consult the published description of the latter group<sup>40</sup>). The most significant findings of this study were that the placebo-adjusted incidences of a type 2 diabetes diagnosis at 10 years showed 34% and 18% reductions for the intensive lifestyle intervention and metformin groups, respectively.<sup>41</sup> Interestingly, while patients in the lifestyle intervention and metformin groups tended to lose weight initially, mean weight of the 3 treatment groups tended to converge at 10 years, though at a range of 0 to  $-2.5$  kg change from baseline for all groups.<sup>41</sup> However, clinicians clearly recognize that lifestyle interventions in most patients are largely ineffective without intensive supervision because it is difficult for most patients to change their lifestyle or maintain positive lifestyle changes. It has been shown that patients with higher perceived and actual risks of developing diabetes did not intend to adopt healthier lifestyle behaviors more readily than those with lower perceived and actual risks,<sup>42</sup> though if followed closely with physician monitoring and clinical support, patients can indeed reap the benefits (eg, risk reduction of developing diabetes) of such alterations.<sup>39-41,43</sup> Unfortunately, intensive treatment approaches are costly<sup>44,45</sup> making them unpopular amidst the current economic crises worldwide and ever rising health care costs in the United States. Some efforts to reduce costs by using community resources or motivational techniques have shown promising results,<sup>46,47</sup> but are far from large-scale implementation.

### Surgical intervention

Obesity, superimposed on a genetic  $\beta$ -cell defect, is the main cause for the increased prevalence of type 2 diabetes.<sup>48</sup> Bariatric surgery is a growing weight loss option for obese people who have failed lifestyle and diet pill interventions. The National Institutes of Health (NIH) guidelines require bariatric surgery candidates to have a body mass index (BMI)  $>40$  kg/m<sup>2</sup> (severe obesity) or a BMI between 35 and

39.9 kg/m<sup>2</sup> with a serious obesity-related health problem such as type 2 diabetes, coronary heart disease, or severe sleep apnea.<sup>49</sup> This is unconscionable considering some health-care providers believe that the NIH guideline should be less restrictive, given the considerable health and cost benefits of bariatric surgery.<sup>50</sup>

Bariatric surgery has dramatic effects on glycemic control. For example, in a randomized controlled trial with 60 obese patients (BMI  $>30$  and  $<40$  kg/m<sup>2</sup>) with type 2 diabetes  $<2$  years, half the patients had laparoscopic adjustable gastric banding with conventional diabetes care; the other half had conventional diabetes therapy with lifestyle changes. Among patients who completed the 2-year follow-up, 73% in the surgical group versus 13% in the control group achieved remission of type 2 diabetes.<sup>51</sup> A 10-year study comparing conventional (nonsurgical) treatment with bariatric surgery showed recovery from diabetes in 72% of patients in the bariatric surgical group, compared with 21% in the nonsurgical group after 2 years.<sup>52</sup> Furthermore, a cost-analysis study indicates that there is a return on investment in 2 to 5 years postsurgery with respect to the costs associated with comorbidities in morbidly obese patients, including those with type 2 diabetes, CAD, hypertension, and sleep apnea.<sup>50</sup> While this strategy is gaining further popularity among patients with BMI  $\geq 35$  kg/m<sup>2</sup>, long-term studies among the dysglycemic subpopulation are needed to ascertain whether this strategy can be applied universally to obese patients with postprandial hyperglycemia.

### Pharmacologic interventions

The classes of drugs for the treatment of type 2 diabetes that primarily target postprandial hyperglycemia are summarized in Table 2.<sup>6,11,53</sup> The 2 newest classes of anti-diabetic agents – dipeptidyl peptidase-4 (DPP-4) inhibitors and glucagon-like peptide-1 (GLP-1) analogs – are incretin-based therapies. The incretin hormones, GLP-1 and glucose-dependent insulinotropic polypeptide (GIP), are released from the small intestine during absorption of meals and increase pancreatic secretion of insulin.<sup>54</sup> GLP-1, but not GIP, suppresses glucagon release from the pancreatic  $\alpha$ -cells. In type 2 diabetes, incretin hormone function is impaired,<sup>54</sup> resulting in less insulin release and more glucagon secretion after meals.<sup>55</sup> More glucose enters the circulation, but there is less efficient glucose removal, higher plasma glucose levels, and hence, acute oxidative stress.<sup>22,55</sup> Disease-related complications associated with oxidative stress may be reduced with agents that target postprandial hyperglycemia.

**Table 2** Profiles of agents currently approved in the US (unless otherwise indicated) primarily targeting postprandial hyperglycemia<sup>6,11,53</sup>

Agent	Mechanism of action	Dosage	HbA <sub>1c</sub> reduction, <sup>a</sup> %	PPG reduction, mmol/L	Adverse effects	Comments/contraindications
<b>Glinides</b>						
1) Repaglinide (Prandin <sup>®</sup> , Novo Nordisk Inc.)	Meglitinide family, short half-life and binds to a SUR1 site, closing K <sub>ATP</sub> channels of the pancreatic β-cells, stimulating insulin release	0.5 mg–2 mg TID, maximum 16 mg daily give 15–30 minutes prior to each meal	~0.6–1.5	~2.6 mmol/L	Hypoglycemia, weight gain	Long residence time on the SUR <sup>53</sup> and prolonged blood glucose-lowering effects if used concomitantly with gemfibrozil
2) Nateglinide (Starlix <sup>®</sup> , Novartis Pharmaceuticals Corporation)	A phenylalanine derivative	120 mg TID; 60 mg TID, give 1–30 minutes prior to each meal	~0.5–0.8	N/A		Lower potential for hypoglycemia, but lower overall glucose-lowering effectiveness
<b>α-Glucosidase inhibitors</b>						
1) Acarbose	Inhibits the terminal step of carbohydrate digestion at the brush border level of the small intestine thereby shifting and delaying absorption	25 mg–100 mg TID prior to each meal	~0.4–0.8	~4.0	Fatulence, abdominal distress or diarrhea	AGIs specifically help PPG, but have little effect on FPG; contraindicated in patients with chronic intestinal conditions, especially inflammatory bowel disease
2) Miglitol (Glyset <sup>®</sup> , Bayer HealthCare Pharmaceuticals Inc.)	Acarbose is largely unabsorbed from the intestine, whereas miglitol is absorbed from the intestine	25 mg–100 mg TID prior to each meal				
<b>GLP-1 analogs</b>						
1) Exenatide (Byetta <sup>®</sup> , Amylin Pharmaceuticals, Inc.)	The analog simulates the activity of GLP-1, namely insulin secretion in a glucose-dependent fashion; inhibits hyperglucagonemia, slows gastric emptying, reduces appetite, and improves satiety, peak of action	5 μg–10 μg BID injections any time within 60 minutes before morning and evening meals	~0.5–1.0	~3.6	Nausea, vomiting, acute pancreatitis	In patients with a history of pancreatitis, other diabetic agents should be considered Can be used as adjunct treatment in patients with type 2 diabetes who take metformin, a sulfonylurea, or a thiazolidinedione, or with a combination of metformin and a sulfonylurea or thiazolidinedione. Decrease in body weight No long-term safety studies at this time
2) Liraglutide (Victoza <sup>®</sup> , Novo Nordisk)		1.8 mg od injection independent of meals	~1.0–1.3 <sup>c</sup>	~1.7–2.7 <sup>c</sup>	As exenatide (above)	As exenatide (above); also use as monotherapy; contraindicated in MTC or multiple endocrine neoplasia syndrome type 2

(Continued)

Table 2 (Continued)

Agent	Mechanism of action	Dosage	HbA <sub>1c</sub> reduction, <sup>a</sup> %	PPG reduction, %	Adverse effects	Comments/contraindications
3) Exenatide sustained release	Expected duration of action ~1 week					Current status: in phase III development
<b>DPP-4 inhibitors</b>						
1) Sitagliptin (Januvia <sup>®</sup> , Merck & Co., Inc.)	Inhibits DPP-4 enzyme, and thereby produces moderate increases in GLP-1 and GIP	100 mg once daily with or without food. In patients with moderate renal insufficiency (CrCL ≥30 to <50 mL/min) reduce dosage to 50 mg daily. In patients with severe renal insufficiency or end-stage renal disease (CrCL is <30 mL/min) reduce dosage to 25 mg daily	~0.6-0.8	~2.8	Upper respiratory tract infection and naso-pharyngitis	No long-term safety studies at this time No serious adverse reactions reported to date Weight neutral
2) Saxagliptin (Onglyza <sup>™</sup> , Bristol-Myers Squibb/AstraZeneca)		2.5 mg or 5 mg once daily regardless of meals 2.5 mg is recommended for patients with moderate or severe renal impairment, or end-stage renal disease (CrCL ≤50 mL/min). 2.5 mg is recommended for patients also taking strong cytochrome P450 3A4/5 inhibitors 50 mg BID, max 100 mg N/A	As sitagliptin (above)	As sitagliptin (above)	As sitagliptin (above)	As sitagliptin (above)
3) Vildagliptin						Current status: approved in Europe
4) Alogliptin						Current status: under FDA review
<b>Rapid-acting insulins</b>						
1) Lispro (Humalog <sup>®</sup> , Eli Lilly and Company)	Suppresses glucose production and increases efficiency of tissue glucose uptake	Individualized	Variable depending on aggressiveness of titration	~11 (not PBO corrected) <sup>b</sup>	Hypoglycemia and weight gain	
2) Aspart (NovoLog <sup>®</sup> , Novo Nordisk)				N/A		
3) Glulisine (Apidra <sup>®</sup> , sanofi-aventis US LLC)				N/A vs PBO		

<sup>a</sup>Assuming an initial HbA<sub>1c</sub> of at least 8%.<sup>b</sup>Lispro (Humalog<sup>®</sup>, Eli Lilly and Company).<sup>c</sup>Exenatide and liraglutide HbA<sub>1c</sub> efficacy based on combination therapy.Data obtained from each product's respective package insert and Nathan DM et al.<sup>6</sup>**Abbreviations:** AGI,  $\alpha$ -glucosidase inhibitor; BID, twice daily; CrCL, creatinine clearance; DPP-4, dipeptidyl peptidase-4; FPG, fasting plasma glucose; GIP, glucose-dependent insulinotropic polypeptide; GLP-1, glucagon-like peptide-1; K<sub>ATP</sub>, potassium adenosine triphosphate; MTC, medullary thyroid carcinoma; PBO, placebo; PPG, postprandial glucose; SUR, sulfonylurea receptor; T1D, 3 times daily.



## GLP-1 analogs

Endogenous GLP-1 is rapidly cleared (1–2 minutes) by the enzyme DPP-4; therefore, the natural form is not practical as a therapeutic intervention in type 2 diabetes management.<sup>56</sup> Injectable GLP-1 analogs are resistant to DPP-4 and thus, have a longer half-life than endogenous GLP-1. GLP-1 analogs increase *glucose-dependent* insulin secretion and decrease glucagon secretion, leading to PPG control, delayed gastric emptying, and increased satiety, potentially leading to weight loss. Exenatide (Byetta<sup>®</sup>, Amylin Pharmaceuticals, Inc.) and liraglutide (Victoza<sup>®</sup>; Novo Nordisk) are injected twice daily and once daily, respectively. Their use in combination lowers HbA<sub>1c</sub> by approximately 0.5% to 1.0%.<sup>6,57</sup> Both agents are approved for use in combination with metformin, a sulfonamide (SU), and/or a thiazolidinedione (TZD); liraglutide is also available as monotherapy in the United States.<sup>6,57</sup> Both agents are associated with gastrointestinal (GI) side effects, including diarrhea, vomiting, and nausea and there is also an association with acute pancreatitis.<sup>6,57</sup> Therefore, the Food and Drug Administration recommends that in a patient with diabetes who has a history of pancreatitis, other antidiabetic agents should be considered.<sup>57,58</sup> For liraglutide, the US prescribing information includes a boxed warning for the risk of thyroid C-cell tumors.<sup>57</sup> A sustained-release form of exenatide, with duration of up to one week is currently in late-phase development.<sup>59,60</sup>

## DPP-4 inhibitors

The DPP-4 inhibitors sitagliptin and saxagliptin were approved in 2006 and 2009, respectively. Vildagliptin, another DPP-4 inhibitor, is currently approved outside the United States. DPP-4 inhibitors, like GLP-1 analogs, mechanistically decrease PPG and have a low propensity for hypoglycemia or weight gain.<sup>61–63</sup> Alogliptin, dutogliptin, and linagliptin are other DPP-4 inhibitors in various stages of development. These DPP-4 inhibitors have been studied as monotherapy as well as in combination with metformin, SUs, and TZDs. DPP-4 inhibitors have fewer GI side effects than GLP-1 analogs.<sup>61,63</sup>

## Rapid-acting insulins

Rapid-acting insulins (lispro, aspart, or glulisine) improve PPG when administered before a meal.<sup>29,64,65</sup> An alternative would be pre-breakfast and pre-dinner premix insulins containing a rapid-acting insulin and a long-acting insulin.<sup>66</sup> These latter insulin regimens, however, are less flexible and are associated with greater risk of hypoglycemia than rapid-acting insulin regimens.<sup>66</sup>

## Guideline update

In 2009, the AACE released a new treatment algorithm. While there were no changes to the placement of insulin in

the algorithm (ie, last line of therapy after oral antidiabetic drug use), the new recommendations advocate the early use of the incretin-based therapies GLP-1 analogues and DPP-4 inhibitors.<sup>67</sup> More specifically, incretin-based therapies are recommended as monotherapy for patients with HbA<sub>1c</sub> 6.5% to 7.5%, which most closely corresponds to the HbA<sub>1c</sub> range previously identified to be most impacted by PPG targeting.<sup>7,28</sup>

## Conclusions

Substantial evidence has accumulated indicating that chronic hyperglycemia is a risk factor for micro- and macrovascular disease. Observational studies indicate that isolated postprandial hyperglycemia increases CV mortality. Various antihyperglycemic agents now exist that preferentially target postprandial hyperglycemia (meglitinides, rapid-acting insulin analogs, GLP-1 agonists, and DPP-4 inhibitors) and afford physicians a choice of treatment options that can now be based on individual patient profiles. Controlling and achieving target goals early in the course of diabetes has been shown to provide better outcomes in terms of CV risk. Postprandial glucose should be normalized along with FPG to achieve the currently recommended goal of HbA<sub>1c</sub> <7%. As reflected in recent trials, a less intense goal may be needed for certain subpopulations of patients with diabetes who have a history of severe CVD, severe hypoglycemia, advanced age, or advanced microvascular or macrovascular complications. Target levels of glucose control should be individualized by focusing on both FPG and PPG and by optimizing other risk factors of CVD, including high blood pressure, hyperlipidemia, obesity, smoking, and poor exercise and dietary habits.

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