Special Issue on diabetes

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Introduction

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Dr Brunton disclosed that he is on the advisory boards of Novo Nordisk Inc., Kowa Pharmaceuticals America, Inc., and Amylin Pharmaceuticals, Inc.

TARGET AUDIENCE
Family physicians and clinicians who have an interest in treating patients with diabetes.

DISCLOSURE STATEMENT
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The prevalence of type 2 diabetes mellitus (T2DM) is rising dramatically. In 1994, only one US state had a T2DM prevalence of ≥6.0%. In 2008, 47 US states had a prevalence of ≥6.0%. In fact, in 2008, the prevalence of T2DM was ≥9.0% in 13 US states. Overall, it is estimated that 23.6 million children and adults—7.8% of the US population—have T2DM. Furthermore, another 57 million people are estimated to have prediabetes.

As a family physician, you and your primary care colleagues provide care to the vast majority of people with T2DM, as well as those with prediabetes. You are, therefore, in an opportune position to make a huge difference in altering the course of this growing epidemic and its consequences. To help you in this critical role, the Primary Care Education Consortium and the Primary Care Metabolic Group have developed this supplement on T2DM.

In this supplement, 5 key topics are included: obesity, postprandial glucose (PPG), diabetic peripheral neuropathic pain (DPNP), diabetic dyslipidemia, and the incretins. Each article is written in a practical manner to provide you with the information you need to help improve the outcomes of your patients with T2DM.

The contribution of obesity to T2DM is well established, and the growing obesity epidemic portends grim consequences, extending beyond T2DM to include other diseases, such as heart disease—unless lifestyle changes are made and sustained. Dr Bestermann provides insight as to how this might be achieved.

Although the management of T2DM typically focuses on glycosylated hemoglobin and fasting plasma glucose levels, PPG plays a critical role in affecting long-term patient outcomes. Using a case-based approach, Dr Reid offers guidance on selecting among the available glucose-lowering therapies to correct postprandial hyperglycemia.

Neuropathic pain is commonly observed in patients with T2DM, causing significant patient morbidity and disability. Dr Kuritzky reviews the adjuvant analgesics commonly used, focusing on how to initiate therapy based on patient characteristics, as well as to modify therapy based on patient response.

Dyslipidemia is common in patients with T2DM, further increasing the risk of cardiovascular disease. The statins, which play a central role in the treatment of dyslipidemia, are the focus of Dr Toth’s article, in which he takes a question-and-answer approach to review how best to use the statins to achieve the recommended lipid goals in patients with T2DM.

Among the treatment options that have recently become available, the incretin group that includes the glucagon-like peptide-1 (GLP-1) agonists and dipeptidyl peptidase-4 (DPP-4) inhibitors offers some important benefits. Dr Unger utilizes a case-based approach to compare the incretins with other glucose-lowering therapies, as well as the differences among the incretins. He also provides the latest information regarding the safety of the 2 GLP-1 agonists and 2 DPP-4 inhibitors currently available in the United States.

I hope you find this supplement helpful as you provide care to your patients with diabetes.

References
Incorporating practical lifestyle management for obesity

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Dr. Bestermann disclosed that he is on the advisory board for Amylin Pharmaceuticals, Inc.

DISCLOSURE STATEMENT
The Primary Care Education Consortium clinical staff have provided financial disclosures and have no conflicts of interest to resolve related to this activity.

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This activity is supported by an educational grant from Amylin Pharmaceuticals, Inc.

LEARNING OBJECTIVES
After reading this article, the primary care clinician should be better able to:

1. List the diabetes-related benefits of weight loss
2. Identify barriers to and facilitators of weight loss
3. Describe the efficacy and safety of orlistat and sibutramine for weight reduction, including impact on cardiovascular and glycemic outcomes
4. Compare the impact on weight of drugs used to lower blood glucose levels

Introduction
Overweight. Obesity. Overnutrition. Call it what you will, but there’s no denying that its prevalence is rising dramatically.1 And while the prevalence of obesity is especially high in nonwhite and low-income people,2 and is generally highest in the southeastern region of the United States,1,3 no demographic is unaffected, including children and teens.4,5 Obesity is a better predictor of undiagnosed type 2 diabetes mellitus (T2DM) than is a family history of diabetes.6 Measures of centralized obesity—specifically, waist-to-height ratio—are better predictors than is body mass index (BMI) for T2DM, hypertension, and dyslipidemia.7

The consequences of obesity are well known. Not only does obesity cost the US economy hundreds of billions of dollars per year;2 it is contributing to the rising prevalence of T2DM and cardiovascular disease8 and the associated morbidity and mortality.

The benefits of weight reduction have been clearly demonstrated. The Diabetes Prevention Program (DPP) demonstrated significant improvements in blood pressure (BP) and lipids,9 as well as C-reactive protein and fibrinogen10 following intensive lifestyle intervention. Reducing body weight to a BMI <30 kg/m² is estimated to reduce the occurrence of myocardial infarction (MI) by 12% and stroke by 2% over a 30-year period, while increasing life expectancy by approximately 1 year. By comparison, reducing BP to <140/90 mm Hg (in people who do not have diabetes) is estimated to reduce the occurrence of MI and stroke by 7% and 11%, respectively, over 30 years while also increasing life expectancy by about 1 year.11

Weight loss is also beneficial for people at risk for T2DM. In people with prediabetes with elevated fasting and postprandial glucose levels, intensive lifestyle management (target >7% weight loss and >150 minutes of physical activity per week) reduced the incidence of T2DM more effectively than did metformin 850 mg twice daily.12 At an average follow-up of 2.8 years, the
incidence of T2DM was 4.8, 7.8, and 11.0 cases per 100 person-years in the lifestyle, metformin, and placebo groups, respectively. In people with diagnosed T2DM, intensive dietary management can provide adequate control of fasting plasma glucose without pharmacologic therapy or reduce the use of antihyperglycemic medications while improving glycemic control. These benefits following weight loss are likely due to a 2- to 3-fold increase in insulin production and significant improvement in the insulin secretory response that parallels moment-to-moment changes in glycemia, as well as reduced insulin resistance.

Significant improvement in health-related quality of life is also observed with weight loss, especially for those with the poorest quality of life at baseline. Significant improvement in health-related quality of life is also observed with weight loss, especially for those with the poorest quality of life at baseline.

Patients at risk for T2DM can be challenging to manage, and usual-care patients generally continue to gain weight. Global risk factor control in patients with T2DM and obese patients is very poor. It is not a question of whether diet and exercise are better than metformin. We do too little too late. Optimal improvement of insulin resistance and its sequelae requires that we use all of the tools at our command in an integrated fashion. Patients need to understand the progressive nature of insulin resistance and the consequences of inaction. Patients with prediabetes should receive the education and support required to improve their diet and exercise regimen. Although metformin is not approved by the FDA for this indication (and will not likely be in the future because of generic availability), consideration might be given to initiating metformin in those who are at very high risk for developing T2DM (combined impaired fasting glucose and impaired glucose tolerance plus other risk factors, such as glycosylated hemoglobin [A1C] >6%, hypertension, low high-density lipoprotein [HDL]-cholesterol, elevated triglycerides, or family history of diabetes in a first-degree relative) and who are obese and under 60 years of age.

**Management of obesity**

**Short- and long-term goals**

Successful management of obesity requires the establishment of reasonable and realistic short- and long-term goals. For example, while normalization of weight may be a reasonable long-term goal in some obese patients, this is not a realistic short-term goal for most obese patients. Instead, weight loss of 1 pound per month may be a more appropriate short-term goal. The key is to establish with the patient a weight loss goal that the patient is committed to achieving over a short period of time, and a plan to achieve that goal. Once that goal has been achieved and the patient can see the benefits of the effort—for example, improvements in glycemic and cardiovascular endpoints and quality of life—the patient may become more motivated to attempt further weight reduction. Failure to establish a realistic goal—which occurs in almost half of patients—can impede long-term outcomes of weight loss programs.

**Barriers to and facilitators of weight loss**

Numerous potential issues affect a person’s body weight, ranging from family and socioeconomic environment to access to and relationships with health care providers. Specific barriers to weight loss include: low motivation, negative peer pressure, a chaotic or unstructured lifestyle, a negative body image, and unrealistic goals. Logistical barriers also must be considered. A survey of inner-city, obese teenagers showed that a fear about personal safety prevented them from engaging in outdoor exercise. On the other hand, a desire to be socially accepted and to prevent future obesity-related medical conditions are motivating factors for losing weight. A good support system is helpful to promote the behavior changes that are usually necessary for weight loss.

Findings of the Study to Help Improve Early Evaluation and Management of Risk Factors Leading to Diabetes (SHIELD) showed that adults with diagnosed T2DM (N=3897) generally know and understand that improving their diet or increasing physical activity will affect their health. However, the majority have not adopted the appropriate behaviors, as evidenced by the small proportion engaging in regular exercise (26%) or following a prescribed dietary plan (33%). These observations, coupled with the wide variety of barriers mentioned previously, underscore the need to communicate to the patient, as well as his or her family, the importance of addressing these barriers and developing an individualized lifestyle management plan.

**Treatment options**

There are 4 general approaches for treating obesity—reducing calories, reducing appetite, increasing energy expenditure, and removing fat—each of which may be considered when developing a management plan (TABLE 1). Although a healthy diet and exercise are the cornerstones of management, pharmacologic therapy also may be necessary. Ideally, the pharmacologic agent selected would target the underlying pathophysiologic mechanisms that contribute to obesity.
Reduction of caloric intake

A conceptually simple—and critically important—approach to weight reduction is reducing caloric intake. Simply reducing caloric intake by 3500 kcal per week (or 500 kcal per day) leads to a weight loss of 1 pound per week. But simply telling patients to reduce calories almost never works in the long term. Emerging evidence tells us that the current tsunami of obesity and related conditions is largely the result of consuming processed foods that combine fat, salt, sugar, and/or highly processed starches. It is not a question of whether we should promote a low-fat or low-carbohydrate diet. Long-term success requires that we carefully instruct patients in how to reduce the consumption of processed carbohydrates, sugar, and fat, especially saturated and trans fat. And although instructing patients to avoid or reduce their consumption of calorie-dense foods and drinks is recommended, patients generally also require assistance with behavior modification.

**Vegetable consumption.** Recent evidence shows an inverse relationship between vegetable consumption and body weight, as vegans (who consume no animal meats or products) were shown to have a lower BMI (23.6 kg/m²) than vegans (who consume no animal meats or products) or nonvegetarians (milk, and milk products; 25.7 kg/m²).25 Furthermore, the risk for T2DM was lower in vegans and lacto-ovo vegetarians than in nonvegetarians (odds ratio, 0.51 and 0.54, respectively). One possible explanation for the lower risk for T2DM in vegans and lacto-ovo vegetarians is that the risk for T2DM decreases with increasing consumption of fiber.26

**Weight loss programs.** Another approach to reducing caloric intake is the use of a commercially available weight loss program. Over 3 months, 69 obese patients with T2DM assigned to the Nutrisystem® D™ (Nutrisystem, Inc., Horsham, PA) program, which provides high-fiber, low-sodium foods with a low glycemic index, lost significantly more weight than did those assigned to a diabetes support and education program (7.1 ± 4% vs 0.4 ± 2.3%, P < .0001). Similar differences were observed with respect to reduction in A1C (−0.88 ± 1.1% vs 0.03 ± 1.09; P < .001).

**Fat restriction.** Orlistat represents a pharmacologic approach to reducing caloric intake. Orlistat interferes with the processing of triglycerides in the stomach and small intestine. Specifically, it inhibits the gastrointestinal (GI) lipases—primarily gastric and pancreatic—that hydrolyze dietary fat (triglycerides) into absorbable free fatty acids and monoglycerides. As a result, GI absorption of dietary fat is reduced by about 30%.26 A meta-analysis of 16 placebo-controlled trials involving 10,631 overweight or obese adults showed that, compared with placebo, orlistat reduced weight by 2.9 kg overall and by 2.3 kg in patients with T2DM over 1 to 4 years.27 The addition of orlistat to a very-low-energy diet (600 to 800 kcal/d) in obese persons with metabolic risk factors such as dyslipidemia, impaired fasting glucose, and diet-treated T2DM has been found to significantly reduce weight regain after 3 years, compared with placebo (4.6 ± 8.6 kg vs 7.0 ± 7.1 kg; P<.02). Furthermore, the incidence of new cases of T2DM was found to be significantly reduced in the orlistat group compared with the placebo group (P=.04).28

Except for GI adverse events, no significant differences were identified between the orlistat and placebo groups. GI adverse events experienced in both the orlistat and placebo groups included fatty/oily stool (23% vs 3%), oily spotting (18% vs 0%), abdominal pain (22% vs 16%), and fecal urgency (9% vs 5%).29

Although these trial results are positive, in our clinic, we have found that side effects from medications interfere with adherence with the entire treatment program. We help patients understand in detail how to restrict fat in the diet rather than routinely prescribe agents that block fat absorption. In addition, we work very hard to minimize side effects.

**Bariatric surgery.** Another approach intended to reduce caloric intake is restrictive bariatric surgery, which has been shown to be among the most effective treatment options compared with lifestyle intervention in producing weight loss (20.7 ± 8.6% vs 1.7 ± 5.2%, respectively) and achieving remission of T2DM (73% vs 13%).29

### Table 1: Methods for treating obesity

<table>
<thead>
<tr>
<th>Goal</th>
<th>Method</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reduction of caloric intake</td>
<td>Low-calorie fat and carbohydrate substitutes; drugs to impair absorption; restrictive bariatric surgery; behavior modification</td>
</tr>
<tr>
<td>Reduction of appetite</td>
<td>Behavior training; anorectic drugs; bypass bariatric surgery; controlling environmental stimuli</td>
</tr>
<tr>
<td>Increase in energy expenditure</td>
<td>Exercise or elevation of metabolic rate (eg, by drug treatment)</td>
</tr>
<tr>
<td>Direct removal of fat</td>
<td>Surgery (liposuction); agents to impair fat storage</td>
</tr>
</tbody>
</table>

meta-analysis by Buchwald et al showed total weight loss in 7258 obese patients with diabetes to be 64% of excess body weight following surgery. Weight loss appeared to last for >2 years.30 Because of its attendant costs and risks, bariatric surgery is best reserved for individuals whose BMI is ≥40 kg/m² or those whose BMI is between 35.0 and 39.9 kg/m² with other comorbidities.31

Reduction of appetite
Another treatment approach is to reduce appetite using sibutramine or phentermine. It should be noted that sibutramine was withdrawn from the market in Europe in January 2010, due to increased risk of MI and stroke when used by patients with heart disease. Although sibutramine remains available in the United States, the FDA has added new warnings that sibutramine should not be used in patients with a history of coronary artery disease, congestive heart failure, arrhythmias, or stroke.32 Consequently, we do not prescribe sibutramine in our clinic.

Phentermine is another appetite suppressant that was often used with fenfluramine until fenfluramine was removed from the US market in 1997. As a single agent, phentermine 15 to 30 mg daily results in an average weight loss of 6.3 kg compared with 2.8 kg with placebo.33 Tolerance to the anorectic effect usually occurs within a few weeks.34

Increase in energy expenditure
Exercise can be effective in reducing weight and improving overall health.14 Even when there is no change or minimal change in body weight, significant benefits are observed. For example, following 16 weeks of progressive resistance training combined with standard care in 62 Latino adults aged >55 years with T2DM, a reduction in A1C of 1.1% has been observed with no change in body weight.35 Similarly, a meta-analysis reviewed 14 studies of exercise interventions (12 aerobic and 2 resistance) in which a total of 504 people with a mean age of 55 years participated. The exercise interventions were at least 8 weeks long, and all studies had control group comparators. The mean A1C reduction was .66%, with a nonsignificant weight loss of .54 kg (P=.76) for those people in the exercise group.36 The reduction in A1C was a result of improvement in glucose homeostasis, coupled with a loss of fat mass and increase in lean mass.37 The American Diabetes Association (ADA) recommends approximately 150 minutes of exercise per week for people with T2DM.37 The ADA notes that resistance and aerobic exercise each provide similar benefits with regard to improved insulin sensitivity, but a greater benefit results from the combination of both forms of exercise. Adherence to an exercise plan is greater when weight loss is recommended by a physician, the exercise plan is developed by the physician and patient together, and the physician provides regular follow-up regarding the exercise plan.38

Other strategies
Other weight loss strategies that have been shown to be associated with a lower BMI in adults with T2DM are regular self-weighing (≥1 time per week), eating breakfast, and minimizing consumption of fast food.39

Special management considerations in T2DM
Given the importance of body weight in the pathogenesis of T2DM, it is essential that body weight be as much a focus of treatment as A1C. Accordingly, in addition to implementing strategies that promote weight loss, the impact on body weight must be considered when selecting both nonpharmacologic and pharmacologic treatments for T2DM and all related conditions. Several of the treatment options available for T2DM promote weight gain (TABLE 2).40 Exceptions include metformin, alpha-glucosidase inhibitors (acarbose, miglitol), and dipeptidyl peptidase-4 inhibitors (sitagliptin, saxagliptin), all of which are weight neutral. Those that promote weight loss include the glucagon-like peptide-1 (GLP-1) agonists (exenatide, liraglutide) and the amylin analog pramlintide, which serves to offset the weight gain associated with insulin. The weight loss observed with the GLP-1 agonists generally ranges from 1 to 4 kg when used as monotherapy41-43 or in combination with other agents.44,45 Agents that are weight neutral or those that promote weight loss may be preferable when weight is an issue.

Our approach to treatment
The clinic where I practice is in a cardiometabolic medical home in Appalachia. Virtually all of our patients have increased risk for cardiovascular events, and the overwhelming majority are obese. Ninety percent are somewhere on the continuum of insulin resistance, prediabetes, or diabetes. Weight and food are the central problems and are the main focus of our efforts. As part of this effort, we talk with patients about their barriers and facilitators to weight loss and work together to address them. Ignoring these practical issues is a recipe for failure.

By far the biggest problem is excess consumption of fat, sugar, and processed high glycemic index carbohydrates. We educate patients to reduce their fat intake to 25% of total calories and saturated fat to 7%, and to dra-
matically restrict sugar and highly processed carbohydrates while increasing their fiber intake.

But stopping there also can be a recipe for failure. It is necessary to provide the patient with specific changes to make. To identify these, the use of a food diary for 1 week can be tremendously helpful. Together with the patient, the food diary can be reviewed and the food choices (and amounts) of greatest concern can be identified. Furthermore, rather than telling the patient to stop eating a certain food, it is often much more effective to reach agreement with the patient to begin by reducing consumption of that food. This approach of behavioral goal setting is far more likely to result in the patient experiencing success and can serve to motivate the patient (and physician), making subsequent lifestyle changes easier.46

Along the same lines, many patients believe that a large amount of weight must be lost in order to accrue any benefit, so they give up before they even start. I suggest reaching an agreement with the patient on a target weight loss of 5% to 7% over a 6- to 9-month period. Again, because achieving small goals is far more effective, I also reach an agreement with the patient on 1 or 2 intermediate steps, such as a 5-pound weight loss in 6 weeks.

In addition to lifestyle interventions, we have found that metformin may be helpful with weight reduction in some patients. We use metformin early in prediabetes, although metformin is not approved for this use. We use insulin early in T2DM, but we work hard to minimize the dose by giving insulin-sparing medications that enhance weight loss or are weight neutral. In our experience, the patient taking 2 insulin shots per day and no metformin gains 10 pounds in a year, compared with modest or no weight change in the patient on metformin and a single self-adjusted shot of basal insulin.

We see patients frequently until they are well controlled and have a good understanding of T2DM and its management. By working closely with the patient, understanding and addressing specific areas of concern, and taking small steps and building on success, we have had patients who were very impaired physically lose impressive amounts of weight.

### Team approach to treatment

The success we have with our patients is the result of a team effort, with the patient as the center of the team. A team approach to fostering patient self-management offers several benefits and should be considered when developing a management plan. In addition to the primary care physician, the team should also include at least a certified diabetes educator and dietitian.46 The reader is referred to the National Standards for Diabetes Self-Management Education developed by the ADA for further details.46

Various team approaches to treatment are possible. An example of this approach was a dietitian-led lifestyle case management intervention program, consisting of individual and group education, support, and referrals over 12 months, which resulted in significantly greater weight loss, reduced waist circumference, and improved health-related quality of life (all, \( P < .001 \)), compared with usual medical care. In 147 patients with obesity and T2DM at 12 months, the between-group difference in weight loss was 3.0 kg; waist circumference, 4.2 cm; and A1C level, 0.19%.47 The total cost, including medical, pharmaceutical, and intervention costs, in the case management group was $3586 lower than in the usual-care group (\( P < .05 \)).48 The lower medical costs in the case management group were mainly the result of fewer hospital admissions. Implementation of the DPP by nurse practitioners in a primary care setting showed similar benefits, including weight loss of ≥5% in 25% of the lifestyle intervention group (N=31) at 9 months.49

### Table 2: Effect of antihyperglycemic agents on body weight40

<table>
<thead>
<tr>
<th>Agent</th>
<th>Effect on body weight</th>
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</thead>
<tbody>
<tr>
<td>Alpha-glucosidase inhibitors (acarbose, miglitol)</td>
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<tr>
<td>Amylin analog (pramlintide)</td>
<td>Decrease</td>
</tr>
<tr>
<td>Dipeptidyl peptidase-4 inhibitors (saxagliptin, sitagliptin)</td>
<td>Neutral</td>
</tr>
<tr>
<td>Glinides (nateglinide, repaglinide)</td>
<td>Increase</td>
</tr>
<tr>
<td>Glucagon-like peptide-1 agonists (exenatide, lixisenatide)</td>
<td>Decrease</td>
</tr>
<tr>
<td>Insulin</td>
<td>Increase</td>
</tr>
<tr>
<td>Metformin</td>
<td>Neutral</td>
</tr>
<tr>
<td>Sulfonylureas (gliclazide, glimepiride, glipizide, glyburide)</td>
<td>Increase</td>
</tr>
<tr>
<td>Thiazolidinediones (pioglitazone, rosiglitazone)</td>
<td>Increase</td>
</tr>
</tbody>
</table>

### References


RESOURCES

Several organizations offer numerous resources that can be helpful in providing patient education, including:

- American Association of Diabetes Educators (http://www.diabeteseducator.org/ProfessionalResources)
- American Diabetes Association (http://www.diabetes.org/food-and-fitness/)
- American Dietetic Association (http://www.eatright.org/Public)
- National Institute of Diabetes and Digestive and Kidney Diseases (http://www2.niddk.nih.gov/HealthEducation/HealthNutrition.htm)
The importance and treatment of postprandial hyperglycemia

**CASE STUDY.** SW is a 56-year-old white male diagnosed with type 2 diabetes mellitus (T2DM) 8 years ago. At diagnosis, therapy was initiated with lifestyle interventions and a sulfonylurea (after the recommendation of metformin as first-line therapy). At the follow-up visit, treatment was intensified to glimepiride 4 mg once daily, metformin 1000 mg twice daily, and pioglitazone 45 mg once daily. SW sees a certified diabetes educator every 3 to 4 months and participates in moderate-intensity exercise 3 to 4 times per week. Despite lifestyle interventions and triple oral therapy, SW’s glycosylated hemoglobin (A1C) remains above the target of <7.0% (Figure 1). His estimated creatinine clearance is 58 mL/min and his eye exam shows grade 1 arteriovenous nicking of the retina. His fasting plasma glucose (FPG) level, drawn at home 3 times per week before breakfast, has ranged from 109 to 141 mg/dL over the past month, while his postprandial glucose (PPG) level, drawn after dinner, has ranged from 178 to 234 mg/dL. SW’s lipid profile remains within the normal range.

**Blood glucose goals**

For patients with T2DM, the American Diabetes Association (ADA) recommends a target A1C level <7.0% and an FPG level between 70 and 130 mg/dL (Table 1). The recommended PPG level, taken 1 to 2 hours after the beginning of a meal, is <180 mg/dL. According to the ADA, glycemic goals should be individualized based on a patient’s duration of diabetes; the age and life expectancy of the patient; comorbidities, especially cardiovascular disease (CVD) and microvascular complications; hypoglycemia unawareness; and individual patient considerations.

SW’s FPG is at times above the target goal of 70 to 130 mg/dL, but his PPG is well above the target goal of <180 mg/dL. Many primary care clinicians find treating PPG to be challenging, and they are reluctant to intensify therapy with treatment that targets PPG, especially prandial insulin. Let’s discuss why the PPG level is important and how to manage it.

**LEARNING OBJECTIVES**

After reading this article, the primary care clinician should be better able to:

1. Explain the relative contribution of fasting plasma glucose and postprandial glucose (PPG) to cardiovascular (CV) risk
2. Describe the impact of lowering PPG on CV function
3. Compare the effectiveness of available agents to lower PPG
4. Identify the best time of day to measure PPG
**Importance of PPG**

Because T2DM is often diagnosed when a patient’s A1C level is 8% to 9% or higher, the initial focus of treatment is on FPG. Research has found that at levels of ≥8.5%, the A1C level is determined more by FPG than by PPG (Figure 2). However, <8.5%, PPG begins to become the major determinant of the A1C level. In fact, as the A1C level falls to <7.3%, it is estimated that PPG contributes approximately 70% to the magnitude of the A1C level.

PPG is important for more than its contribution to the A1C level. Further evidence of the importance of PPG relates to its contribution to atherogenic risk. A meta-analysis of the Whitehall, Paris Prospective, and Helsinki Policemen studies, all of which were large prospective clinical trials investigating the association between high, but nonglabetic, blood glucose levels and the risk of death, showed that men in the upper 20% of the PPG distribution (≥88 mg/dL [Whitehall], ≥140 mg/dL [Paris Prospective], or ≥113 mg/dL [Helsinki Policemen]) had a significantly higher risk of all-cause mortality compared with men in the lower 80%.

In contrast, only men in the upper 2.5% of the FPG distribution (>100 mg/dL [Whitehall], >169 mg/dL [Paris Prospective], or >132 mg/dL [Helsinki Policemen]) had an increased risk of all-cause mortality. In terms of death from CVD and coronary heart disease, men in the upper 2.5% of PPG and FPG distributions were at similar risk. Similar findings were observed in people with or without diagnosed T2DM in the Chicago Heart Association Detection Project in Industry Study and the Diabetes Epidemiology: Collaborative analysis Of Diagnostic criteria in

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### Table: Case study

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>6 mo</th>
<th>1 y</th>
<th>2½ y</th>
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<th>8 y</th>
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<td>FPG, mg/dL</td>
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<td>147</td>
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<td>A1C, %</td>
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<td>BMI, kg/m²</td>
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</tr>
</tbody>
</table>

A1C, glycosylated hemoglobin; BMI, body mass index; FPG, fasting plasma glucose; SU, sulfonylurea; TZD, thiazolidinedione.

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**FIGURE 1**

![Graph](image_url)
Europe (DECODE) study. The DECODE study assessed the risk of death according to glucose category from 13 prospective cohort studies involving more than 25,000 adults aged 30 years or older. The analysis showed that within each FPG group (normal, impaired, or diabetes), mortality increased with increasing 2-hour glucose concentrations. However, for the 2-hour-glucose groups (<140, 141-198, or >198 mg/dL), mortality increased with increasing FPG levels only in the group with normal glucose tolerance.

These results indicate that FPG concentrations alone do not identify individuals at increased risk of death due to hyperglycemia and that PPG provides additional information to identify those at the greatest risk of death due to hyperglycemia. These epidemiologic studies suggest that uncontrolled PPG is an independent risk factor for CVD.

PPG is important for more than its contribution to atherogenic risk; it may also be important because of evidence suggesting improvement in CV function with the lowering of PPG levels. In well-matched, drug-naive patients with T2DM, patients treated with repaglinide 1.5 to 12 mg/d achieved a significantly lower PPG level after 12 months than did those treated with glyburide 5 to 20 mg/d (148 vs 180 mg/dL; \( P < .01 \)), despite similar reductions in A1C levels (0.9%). Furthermore, the carotid intima media thickness decreased 0.029 mm in repaglinide patients vs 0.005 mm in glyburide patients (\( P = .02 \)).

Another investigation found that 8 months after a successful coronary intervention following an acute coronary event, and after receiving subsequent information and dietary recommendations, patients who achieved a PPG level <140 mg/dL after a 75-g oral glucose tolerance test (OGTT) experienced a significant improvement in epicardial flow in the culprit artery. However, in patients whose PPG remained elevated, the epicardial flow was not significantly improved. Further investigation in larger randomized clinical trials is needed.

The mechanism whereby elevated PPG exerts its effects on atherogenesis is unknown, but it may be through a negative impact on endothelial function. Nonetheless, because of its contribution to glycemia and the A1C level, as well as atherogenesis, the importance of achieving PPG targets is clear.

### Lifestyle interventions to reduce PPG

Lifestyle interventions remain a cornerstone of therapy for lowering PPG in T2DM. A 3-year randomized controlled study of lifestyle interventions, including dietary modification and exercise, with the objective of a 5% to 7% weight loss, was undertaken in people with an FPG level <140 mg/dL and a glucose level of 140 to 225 mg/dL 2 hours following 2 OGTTs. After 1 year, PPG levels decreased 11 mg/dL in the lifestyle intervention group and increased 7 mg/dL in the control group, while the A1C levels decreased 0.24% and 0.19%, respectively. Other measures of glycemic control, including fasting insulin concentration and the homeostasis model assessment of insulin resistance (HOMA-IR), as well as free fatty acid levels, were reduced in the lifestyle intervention group. After 3 years, a sustained reduction of the PPG level was observed, but only in the 72% (106/147) who completed the 3-year study.

### CASE STUDY

The sustained elevation of SW’s PPG level, despite significant lifestyle interventions, triple oral therapy, and some evidence of early vascular complications, indicates that SW’s therapy needs to be changed. Because the combination of pioglitazone plus metformin has been shown to be more effective in lowering PPG than either agent alone or the combination of glimepiride plus metformin, discontinuing glimepiride is reasonable. The question becomes: What therapy should be initiated? In answering this question, other factors need to be considered, such as effect on body weight, side effects, tolerability, patient acceptance, and cost.

### Pharmacologic options to reduce PPG

Several pharmacologic options are available that reduce PPG levels. In the case of SW, he is already taking glimepiride, metformin, and pioglitazone. Since the addition of another oral agent would not be recommended, the option is to either switch oral agents or add insulin. Because the available oral agents have not been directly

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**TABLE 1  American Diabetes Association recommended glucose goals**

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Goal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glycosylated hemoglobin (A1C)</td>
<td>&lt;7.0%</td>
</tr>
<tr>
<td>Preprandial or fasting plasma glucose</td>
<td>70-130 mg/dL</td>
</tr>
<tr>
<td>Postprandial glucose (1-2 hours after the beginning of a meal)</td>
<td>&lt;180 mg/dL</td>
</tr>
</tbody>
</table>


---
compared across the spectrum of patients with T2DM (drug treatment–naïve, metformin failure, obese vs non-obese, or A1C >10% vs >8%, etc), determining which oral agent should be discontinued and which new oral agent to add is not clear.

Each of the 3 agents SW is currently taking reduces PPG. The reduction in PPG with metformin, for example, has been shown to be comparable to glyburide, using average daily doses of 1796 mg and 7.6 mg, respectively (N=315). From a baseline PPG of 232 and 251 mg/dL, respectively, PPG decreased 70 mg/dL with metformin and 63 mg/dL with glyburide after 16 weeks.11 Similarly, metformin 1000 mg twice daily has been shown to provide similar reduction in PPG compared with repaglinide 2 mg 3 times daily in non-obese, insulin-naive patients with T2DM (N=96). After 1 month of treatment, PPG decreased approximately 55 mg/dL after a standard meal with each treatment.12

The alpha-glucosidase inhibitors are effective in lowering PPG because they delay carbohydrate absorption, with one meta-analysis reporting mean reductions of 42 and 49 mg/dL for acarbose and miglitol, respectively.13 The alpha-glucosidase inhibitors have the added advantage of being weight neutral; however, gastrointestinal side effects often limit patient acceptance.

The glinides are another option. Repaglinide has been shown to provide a similar reduction in PPG (P=.07) compared with glyburide after 14 weeks in 195 patients with T2DM.14 Compared with glimepiride 2 mg once daily, repaglinide 1 mg twice daily has been shown to provide a significantly greater reduction in PPG following a standard meal (N=14).15 An 8-week study involving 101 patients showed similar reduction of PPG with nateglinide 120 mg 3 times daily and glyburide 10 mg once daily following a standard meal.16 Direct comparison of repaglinide and nateglinide shows comparable reduction in PPG.17,18 After 12 weeks, the reduction in PPG was 72 mg/dL with repaglinide 1 mg 3 times daily and 69 mg/dL with nateglinide 90 mg 3 times daily following a standard meal (N=230).17

Other options include the oral dipeptidyl peptidase-4 (DPP-4) inhibitors sitagliptin19 and saxagliptin.20 In addition, injectable agents are also effective in lowering PPG. These include the glucagon-like peptide-1 (GLP-1) agonists exenatide10,21,22 and liraglutide,23 the amylin analog pramlintide,24,25 and prandial insulin.26 An advantage of the GLP-1 agonists is that they promote weight loss. Pramlintide is approved only for use in conjunction with prandial insulin.25 [For further discussion of the DPP-4 inhibitors and GLP-1 agonists, see “Choosing among the incretin agents and why it matters” on page S30.]

As noted previously, the addition of insulin to SW’s current regimen is an alternative to switching oral therapy. Insulin is the most effective agent available for low-
erating both FPG and PPG.\textsuperscript{10} Basal insulin is generally more effective in reducing FPG; prandial or mealtime insulin is more effective in reducing PPG. Basal insulins include neutral protamine Hagedorn and the long-acting insulin analogs detemir and glargine. The prandial insulins include regular human insulin and the rapid-acting insulin analogs aspart, glulisine, and lispro.

Holman et al identified the effects of different insulin analog regimens on A1C and other measures of glucose control, including PPG.\textsuperscript{26} This 3-year, open-label, multicenter trial included 708 patients who had suboptimal glycemic control (A1C $\geq$8.5%) while taking metformin and a sulfonylurea. Patients were randomized to biphasic insulin aspart twice daily, prandial insulin aspart 3 times daily, or basal insulin detemir once or twice daily. The median doses were 0.78, 0.94, and 1.03 unit/kg/d, respectively (TABLE 2). At the end of 3 years, A1C levels were 7.1%, 6.8%, and 6.9% in the biphasic, prandial, and basal insulin groups, respectively ($P$=.28). However, the decrease in PPG was significantly greater in the prandial insulin group. From a baseline of 227 mg/dL, PPG decreased 61, 85, and 67 mg/dL in the biphasic, prandial, and basal insulin groups, respectively ($P$<.001 biphasic vs prandial; $P$=.04 biphasic vs basal; $P$=.007 prandial vs basal). The rates of grade 2 or 3 hypoglycemia were 3.0, 5.7, and 1.7 per patient/year ($P$<.001 biphasic vs prandial; $P$<.001 biphasic vs basal; $P$<.001 prandial vs basal).

This study demonstrated that the highest rate of hypoglycemic events occurred in the prandial arm, and it reminds us that when using insulin, it is important to balance the patient’s need for glucose lowering with the risk of hypoglycemia and weight gain. Beyond insulin, there are many other factors affecting hypoglycemia and weight gain, such as physiology, food intake, and physical activity.

### CASE STUDY
As recommended by the 2009 ADA consensus guidelines,\textsuperscript{10} the physician suggested that SW start insulin. Because the physician had talked with him about the role and importance of insulin, SW agreed to begin insulin with appropriate education. How should insulin therapy be initiated?

### Initiating insulin therapy
Initiating insulin is best done in the context of a diabetes care team. The patient, primary care clinician, diabetes educator, and dietitian all play a critical role in successful transition to insulin therapy. Most communities have diabetes education programs either through a local hospital or a community health center. Organizations such as the American Association of Diabetes Educators are helpful for locating a certified diabetes educator in your area (http://www.diabeteseducator.org/DiabetesEducation/Find.html). It is important to work with your patient to see that he or she receives the full benefit of the services provided in such a program.

As suggested by the study by Holman et al,\textsuperscript{25} insulin can be initiated as basal insulin once or twice daily, prandial insulin with ≥1 meals, or biphasic insulin once or more daily. Basal insulin would be the best choice if the plan is to lower both PPG and FPG and replace pioglitazone within a few months. However, it must be recognized that control of PPG is less likely with basal insulin than with prandial insulin. From a physiologic viewpoint, prandial (mealtime or bolus) insulin would be the best choice if the plan is to target PPG and to continue the oral agents (metformin and pioglitazone). The sulfonylurea (glimepiride) should be discontinued when starting prandial insulin.\textsuperscript{19} However, prandial insulin is generally used in combination with basal insulin. Consequently, a combination of basal and bolus insulins could be initiated to control both FPG and PPG with the goal of discontinuing pioglitazone. For the same reasons, biphasic insulin could be started, although this approach makes it unappealing to many patients.

### TABLE 2
Outcomes and changes from baseline at 3 years\textsuperscript{26}

<table>
<thead>
<tr>
<th></th>
<th>Biphasic</th>
<th>Prandial</th>
<th>Basal</th>
<th>$P$ value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>insulin</td>
<td>insulin</td>
<td>insulin</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Biphasic vs prandial</td>
</tr>
<tr>
<td>Median dose (unit/kg/d)</td>
<td>0.78</td>
<td>0.94</td>
<td>1.03</td>
<td>.05</td>
</tr>
<tr>
<td>$\triangle$ A1C (%)</td>
<td>-1.3</td>
<td>-1.4</td>
<td>-1.2</td>
<td>NR</td>
</tr>
<tr>
<td>$\triangle$ PPG (mg/dL)</td>
<td>-61</td>
<td>-85</td>
<td>-67</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Grade 2/3 hypoglycemia (events/patient/year)</td>
<td>3.0</td>
<td>5.7</td>
<td>1.7</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>$\triangle$ Body weight (kg)</td>
<td>5.7</td>
<td>6.4</td>
<td>3.6</td>
<td>.21</td>
</tr>
</tbody>
</table>

A1C, glycosylated hemoglobin; BMI, body mass index; NR, not reported; PPG, postprandial glucose.

difficult to modify the dose to achieve control of both FPG and PPG at the same time.

For most patients, an average total daily dose of insulin is 0.6 to 0.7 unit/kg/d or ~40 to 50 units/d for a 70 kg person, although this is subject to many factors, such as degree of insulin resistance, baseline glycemia, and duration of T2DM. Approximately half of the insulin required each day is for basal glycemia and the other half is for mealtime glycemia. Thus, approximately 20 to 25 units of basal insulin and 20 to 25 units of prandial insulin will be required for glycemic control.

Although there are several approaches that can be followed to determine the initial insulin dose, the admonition to start low and titrate is advisable. For prandial insulin, an initial dose of 0.05 to 0.1 unit/kg per meal is reasonable, although 0.1 unit/kg can be used for the largest meal. For basal insulin, 0.15 to 0.2 unit/kg/d, or 10 units either once daily or twice daily, is reasonable. Patients whose pre-breakfast or pre-dinner plasma glucose level is <126 mg/dL or who have a body mass index <26 kg/m² might be started with 6 units of basal insulin twice daily. Close monitoring of blood glucose levels, with titration of prandial and/or bolus insulin will be needed. Adjustment of the doses of other antihyperglycemic agents may also be necessary.

**Summary**

PPG is an important target to address in the overall management of T2DM. Lifestyle interventions play an important role in PPG control, as well as global diabetes management goals. Oral antihyperglycemic agents lower PPG to varying degrees. Our most powerful treatment option to address PPG is prandial insulin. Collaboration between patient, primary care clinician, diabetes educator, and diettian is critical to successful initiation of insulin therapy.

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**References**

Managing diabetic peripheral neuropathic pain in primary care

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Dr Kuritzky disclosed that he is on the advisory board for Eli Lilly and Company, Endo Pharmaceuticals Inc., Novo Nordisk Inc., and PriCara, division of Ortho-McNeil-Janssen Pharmaceuticals, Inc.

Introduction
Results of a 2005 survey by the American Diabetes Association (ADA) show that diabetic peripheral neuropathic pain (DPNP) is highly under-recognized: only 1 in 4 people with symptoms of diabetic peripheral neuropathy (DPN) has been diagnosed with the condition. Neuropathic pain is common in patients with type 2 diabetes mellitus (T2DM), with one report indicating a prevalence of 16.2%, compared with 4.9% in people without T2DM ($P<.0001$). The impact of DPN is substantial, as it can lead to significant morbidity, poor quality of life, decreased productivity, and increased health care utilization and medication use. DPN and DPNP are not, however, simply quality of life issues. T2DM is the number one cause of atraumatic limb loss in the United States, and DPN is the most

CONTINUING MEDICAL EDUCATION

TARGET AUDIENCE
Family physicians and clinicians who have an interest in treating patients with diabetes.

LEARNING OBJECTIVES
After reading this article, the primary care clinician should be better able to:
1. Evaluate patients with type 2 diabetes mellitus (T2DM) for symptoms that may be indicative of diabetic peripheral neuropathic pain (DPNP)
2. Describe the pathophysiology of DPNP
3. Outline clinical guideline-based pharmacologic treatment for DPNP
4. Make recommendations for monitoring patients with DPNP, including the signs and symptoms to assess when treatment is modified

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common etiology. Indeed, one study of Native Americans found an 8-year amputation rate of 4.4%, while another prospective evaluation found a 5-year mortality rate of 27% from the time of diagnosis of diabetic foot ulcers.

**Pathogenesis of diabetic neuropathy**

DPN is categorized as one of the microvascular complications of T2DM, grouped with retinopathy and nephropathy. This categorization reflects the idea that DPN results from nerve dysfunction secondary to disease of the vasonervorum, the microvasculature to the nerves. Poor blood flow in nerves has been observed to contribute to a failure to raise nerve conduction velocities immediately after exercise, possibly as a result of nerve hypoxia. Possible vascular causes include nerve hypoxia, epineurial vessel atherosclerosis, and increased oxygen free radical activities. Some treatment modalities capitalize on this putative mechanism to treat DPNP. However, the exact pathogenesis of DPN remains unclear, and may involve metabolic disturbance and vascular dysfunction. Proposed metabolic etiologies include accumulation of sorbitol, reduced neural L-carnitine levels, impaired essential fatty acid and prostaglandin metabolism, and excessive glycogen accumulation.

**Diagnosing diabetic neuropathy**

Distal symmetrical polyneuropathy, the most common type of diabetic neuropathy, may be sensory or motor in nature and may involve small or large fibers, or both. Small-fiber disease typically precedes large-fiber disease, and sensory symptoms usually precede motor symptoms. A stocking/glove pattern is characteristic of the sensory impairment, which is seen both more commonly and earliest in the lower extremities, particularly in the feet. Since the longest peripheral nerves are involved first, lower extremity involvement occurs first, but (uncommonly) upper extremity symptoms may be contemporaneous with lower extremity symptoms. Rarely, upper extremity involvement without lower extremity symptoms may occur.

Large-fiber neuropathy typically causes painless paresthesias with impairment of vibration, but may also include proprioceptive dysfunction, altered touch and pressure sensations, and loss of ankle reflexes. Large-fiber dysfunction is significantly correlated with cardiovascular risk factors, including male gender, hypertension, elevated total and low-density lipoprotein cholesterol, smoking, and being overweight. By comparison, small-fiber neuropathy is characterized by pain, burning, and impairment of pain and temperature sensations. Although nerve conduction is slowed in large-fiber neuropathy, nerve conduction is usually normal in small-fiber neuropathy.

To preliminarily assess the presence of DPNP, simply asking a patient, “Do your feet burn, hurt, or tingle?” is a reasonable starting point. To confirm a diagnosis of DPNP, the presence of DPN must be established. This is important because other factors that contribute to or cause neuropathic pain are common in patients with T2DM. One study found that 53% of patients with T2DM had at least one additional potential cause for distal sensory polyneuropathy, including use of neurotoxic medications, alcohol abuse, vitamin B12 deficiency, and renal disease.

A variety of simple, as well as highly sophisticated, evaluation tools are available to evaluate peripheral nerve function. Although monofilament testing has been the most popular tool in primary care, a simple test using a 128-Hz tuning fork can be performed. The tuning fork has recently been shown to provide superior predictive value compared with monofilaments.

Vibration testing using the 128-Hz tuning fork determines whether vibration sense is normal, impaired, or absent. Testing is performed by first activating the tuning fork by striking against a hard object and demonstrating to the patient how you apply it to your own bony prominence (eg, wrist, elbow, etc). Next, the vibrating fork is applied to a bony prominence where it is not likely that the patient has neuropathy, such as the hand, elbow, or wrist. If vibration is not detected (since patients with T2DM can harbor both upper and lower extremity neuropathy), place the tuning fork somewhere sufficiently central that vibration will be felt, such as the chin or forehead. Once the patient is acquainted with the vibration experience he or she is supposed to report on, place the vibrating fork on the metatarsophalangeal joint. If no vibration is felt, the patient has *absent* vibration sense, and has peripheral neuropathy. If vibration is felt, ask the patient to tell you when vibration *stops*. Immediately upon notification that vibration has stopped, place the tuning fork on *your* wrist; if you still feel vibration when the patient has told you that the vibration has stopped, the patient has *impaired* vibration sense.

Once the presence of distal symmetrical polyneuropathy has been established—in the absence of other etiologies for neuropathy—one may make a provisional diagnosis of DPN. Because of the insidious nature of this condition, patients may not be aware of its impact on their
health and how they may have adapted (eg, patients may avoid exercise due to exacerbation of discomfort induced by activity).

Not all patients with DPN experience DPNP, although pain is a common reason for patients with DPN to seek medical care. DPNP is often described as burning, pins and needles, tingling, shooting, deep aching, jabbing, stabbing, or cold. Pain can be unprovoked and/or worsened by activity. DPNP is often worse at night, thereby compromising sleep and causing next-day fatigue. Alloodynia, or pain in response to a stimulus that is not normally painful, may also be described.

The use of validated pain rating scales can be helpful to assess the presence and characteristics of pain. Examples of these rating scales include the Leeds Assessment of Neuropathic Symptoms and Signs,\textsuperscript{17} the Neuropathic Pain Scale,\textsuperscript{18} the Neuropathic Pain Questionnaire,\textsuperscript{19} and the Brief Pain Inventory for Diabetic Peripheral Neuropathy.\textsuperscript{20} One tool that includes severity, time of day, and least/average/worst, to assist in targeting treatment to the time of greatest pain burden is available. [To view this tool, please see the electronic version of this supplement at: http://www.jfptonline.com/supplements.asp?id=8554.]

### Diagnostic tips
- Conduct the physical examination beginning from the feet and working upward
- Watch patients ambulate at each visit
- Use a 128-Hz tuning fork to assess for the presence of distal symmetrical polyneuropathy
- Investigate other causal or contributing factors
- Inquire about activities of daily living, sleep, depression, or obstacles to successful exercise

### Treatment of diabetic neuropathy
While it may be tempting to focus on symptomatic management of DPNP, it is vital that treatment be initiated in the context of the whole patient, a process that should be accomplished in collaboration with the patient. The patient’s poor glycemic control is almost certainly contributing to the DPNP, since the glycosylated hemoglobin (A1C) level and neuropathy are linearly related. Therefore, it is important to reinforce the patient’s glycemic goals and the health benefits in achieving them, and to reassess his or her lifestyle interventions and medications. Other factors that might contribute to the DPNP should be investigated and managed. Education about risk factors such as hypertension, dyslipidemia, smoking, and body weight, should be provided and treatment plans developed, as appropriate. Interestingly, in the United Kingdom Prospective Diabetes Study, tight blood pressure control was as or more effective than standard glucose control in reduction of aggregate microvascular events.\textsuperscript{21}

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### Table 1: Pharmacologic treatment options\textsuperscript{12,26,28,29}

<table>
<thead>
<tr>
<th>First-line</th>
<th>Second-line</th>
<th>Third-line</th>
</tr>
</thead>
</table>
| • Calcium channel alpha\textsubscript{2}-delta ligands  
  – Gabapentin  
  – Pregabalin\textsuperscript{*}  
• Serotonin-norepinephrine reuptake inhibitors  
  – Duloxetine\textsuperscript{*}  
  – Venlafaxine ER  
• Topical lidocaine  
  – 5% lidocaine patch  
• Tricyclic antidepressants  
  – Secondary amines  
    • Nortriptyline  
    • Desipramine  
  – Tertiary amines  
    • Amitriptyline  
    • Imipramine  | • Opioid agonists  
  – Morphine  
  – Oxycodone CR  
  – Methadone  
  – Levoamphetamine  
  – Hydromorphone  
  • Tramadol  | • Anticonvulsants  
  – Carbamazepine  
  – Lamotrigine  
  – Oxcarbazepine  
  – Phenytoin  
  – Topiramate  
  – Valproic acid  
• Antidepressants  
  – Bupropion  
  – Citalopram  
  – Paroxetine  
• Antiarrhythmic  
  – Mexiletine  
• Capsaicinoid  
  – Topical capsaicin  |

\textsuperscript{*}Approved for treatment of diabetic peripheral neuropathic pain by US Food and Drug Administration.
### Table 2: Dosing considerations for first- and second-line agents

<table>
<thead>
<tr>
<th>Medication class</th>
<th>Starting dosage</th>
<th>Titration</th>
<th>Maximum dosage</th>
<th>Duration of adequate trial</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Secondary amine TCAs</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nortriptyline, desipraminea (use a tertiary amine TCA only if a secondary amine TCA is not available) 25 mg at bedtime</td>
<td>Increase by 25 mg daily every 3-7 days as tolerated</td>
<td>150 mg daily; if blood level of active medication and its metabolite is below 100 ng/mL (mg/mL), continue titration with caution</td>
<td>6-8 weeks with at least 2 weeks at maximum tolerated dosage</td>
<td></td>
</tr>
<tr>
<td><strong>SSNRIs</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Duloxetine</td>
<td>30 mg once daily</td>
<td>Increase to 60 mg once daily after one week</td>
<td>60 mg twice daily</td>
<td>4 weeks</td>
</tr>
<tr>
<td>Venlafaxine</td>
<td>3.75 mg once or twice daily</td>
<td>Increase by 75 mg each week</td>
<td>225 mg daily</td>
<td>4-6 weeks</td>
</tr>
<tr>
<td><strong>Calcium channel alpha2-delta ligands</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gabapentin</td>
<td>100-300 mg at bedtime or 100-300 mg three times daily</td>
<td>Increase by 100-300 mg three times daily every 1-7 days as tolerated</td>
<td>3600 mg daily (1200 mg three times daily); reduce if impaired renal function</td>
<td>3-8 weeks for titration plus 2 weeks at maximum dosage</td>
</tr>
<tr>
<td>Pregabalin</td>
<td>50 mg three times daily or 75 mg twice daily</td>
<td>Increase to 300 mg daily after 3-7 days, then by 150 mg/d every 3-7 days as tolerated</td>
<td>600 mg daily (200 mg three times daily or 300 mg twice daily); reduce if impaired renal function</td>
<td>4 weeks</td>
</tr>
<tr>
<td><strong>Topical lidocaine</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5% lidocaine patch</td>
<td>Maximum of 3 patches daily for a maximum of 12 h</td>
<td>None needed</td>
<td>Maximum of 3 patches daily for a maximum of 12-18 h</td>
<td>3 weeks</td>
</tr>
<tr>
<td><strong>Opioid agonists</strong>c</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Morphine, oxycodone, methadone, levorphanola</td>
<td>10-15 mg morphine every 4 h or as needed (equianalgesic dosages should be used for other opioid analgesics)</td>
<td>After 1-2 weeks, convert total daily dosage to long-acting opioid analgesic and continue short-acting medication as needed</td>
<td>No maximum dosage with careful titration; consider evaluation by pain specialist at relatively high dosages (eg, 120-180 mg morphine daily; equianalgesic dosages should be used for other opioid analgesics)</td>
<td>4-6 weeks</td>
</tr>
<tr>
<td>Tramadol</td>
<td>50 mg once or twice daily</td>
<td>Increase by 50-100 mg daily in divided doses every 3-7 days as tolerated</td>
<td>400 mg daily (100 mg four times daily); in patients older than 75 y, 300 mg daily</td>
<td>4 weeks</td>
</tr>
</tbody>
</table>

**SSNRI**, selective serotonin and norepinephrine reuptake inhibitor; **TCA**, tricyclic antidepressants.

aConsider lower starting dosages and slower titration in geriatric patients.
bFirst-line only in certain circumstances.
cConsider lower starting dosages and slower titration in geriatric patients; dosages given are for short-acting formulation.

Pain management: Pathogenetic mechanisms

Many drugs have been studied for the treatment of DPNP, including aldose reductase inhibitors, vasodilators, angiotensin-converting enzyme inhibitors, vitamin E, alpha-lipoic acid, and acetyl-L-carnitine. Although alpha-lipoic acid and acetyl-L-carnitine have not been approved by the FDA for DPNP, their use is supported by randomized clinical trials.

Alpha-lipoic acid has been shown to reduce the severity of symptoms in DPNP. A meta-analysis of 4 randomized clinical trials involving 1258 patients found significant improvement in the responder rate (those who achieved ≥50% improvement in the Total Symptom Score) with IV alpha-lipoic acid, compared with placebo after 3 weeks (52.7% vs 36.9%; P < 0.05). One singular outcome of the Symptomatic Diabetic Neuropathy (SYDNEY) trial was an actual improvement in nerve conduction, signifying potential improvement in nerve function, as opposed to simply relieving DPN symptoms. No other intervention has been convincingly shown to improve nerve function in DPNP.

Subsequently, the SYDNEY 2 trial involving 181 patients demonstrated significant improvement in pain, paresthesias, and numbness after 5 weeks with oral alpha-lipoic acid 600 mg once daily, providing the optimum risk-benefit ratio. A reduction of ≥50% in the Total Symptom Score was observed in 62% of patients treated with alpha-lipoic acid 600 mg, 50% with 1200 mg, 56% with 1800 mg, and 26% for placebo (P < 0.05 for each vs placebo). Compared with placebo, incidence rates of the most common adverse events were nausea (0% vs 13%; P < 0.05), vomiting (0% vs 2%; P = NS), and vertigo (0% vs 4%; P = NS), respectively.

<table>
<thead>
<tr>
<th>Table 3</th>
<th>When to avoid specific first- and second-line treatment options</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Situation</strong></td>
<td><strong>Avoid</strong></td>
</tr>
<tr>
<td><strong>Medical comorbidities</strong></td>
<td></td>
</tr>
<tr>
<td>Glaucoma</td>
<td>Duloxetine, tricyclic antidepressants</td>
</tr>
<tr>
<td>Orthostatic hypotension</td>
<td>Duloxetine, oxycodone CR, tricyclic antidepressants</td>
</tr>
<tr>
<td>Cardiac or electrocardiographic abnormality</td>
<td>Tricyclic antidepressants</td>
</tr>
<tr>
<td>Hypertension</td>
<td>Duloxetine, tricyclic antidepressants</td>
</tr>
<tr>
<td>Renal insufficiency</td>
<td>Duloxetine, gabapentin, oxycodone CR, pregabalin, tramadol</td>
</tr>
<tr>
<td>Hepatic insufficiency</td>
<td>Duloxetine, oxycodone CR, tramadol</td>
</tr>
<tr>
<td>Respiratory depression</td>
<td>Oxycodone CR, tramadol</td>
</tr>
<tr>
<td>Falls or balance issues</td>
<td>Pregabalin, tricyclic antidepressants</td>
</tr>
<tr>
<td>Erectile dysfunction</td>
<td>Duloxetine, oxycodone CR, pregabalin, tricyclic antidepressants</td>
</tr>
<tr>
<td><strong>Psychiatric comorbidities</strong></td>
<td></td>
</tr>
<tr>
<td>Depression</td>
<td>Oxycodone CR, pregabalin</td>
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<tr>
<td>Anxiety</td>
<td>Gabapentin, oxycodone CR, tramadol</td>
</tr>
<tr>
<td>Suicidal ideation</td>
<td>Duloxetine, gabapentin, oxycodone CR, pregabalin, tramadol, tricyclic antidepressants</td>
</tr>
<tr>
<td><strong>Other factors</strong></td>
<td></td>
</tr>
<tr>
<td>Abuse potential</td>
<td>Oxycodone CR, tramadol</td>
</tr>
<tr>
<td>Drug Interactions</td>
<td>Duloxetine, tricyclic antidepressants</td>
</tr>
<tr>
<td>Weight gain</td>
<td>Pregabalin, tricyclic antidepressants</td>
</tr>
<tr>
<td>Edema</td>
<td>Gabapentin, pregabalin</td>
</tr>
</tbody>
</table>

*Contraindicated in uncontrolled narrow-angle glaucoma.

Avoid if creatinine clearance <30 mL/min.

Reduce dose if creatinine clearance <60 mL/min.

Reduce dose if creatinine clearance <30 mL/min.
Acetyl-L-carnitine, which is deficient in the neural fibers of patients with T2DM, has been shown in 2 randomized clinical trials to increase the number of sural nerve fibers and to regenerate nerve fiber clusters. Patients (N=1257) received acetyl-L-carnitine 1000 mg 3 times daily for 52 weeks. Although nerve conduction velocities and amplitudes did not improve, vibration perception did, and pain reduction was observed, especially in those with A1C levels >8.5%.25

### Pain management: Symptom reduction

Chronic pain patients often indicate that a 30% reduction of pain from baseline is "meaningful," and a ≥50% reduction is "marked improvement."26 It is important to discuss with patients the pain features that are most troublesome for them, or a function or activity of daily living that is most disrupted by their pain. For instance, analgesic pharmacotherapy targeted to nocturnal increases in pain may provide both pain relief and sleep improvement, and may not necessarily be continued at the same dosage during waking hours when pain may not be as problematic. Pain and depression are commonly interwoven, and patients who experience both achieve remission less often, take longer to do so, and relapse more often and more quickly. Hence, treating consequences of pain, such as depression and sleep disorders, is also important.

Although anti-inflammatory agents are the mainstay of therapy for nociceptive pain (eg, mechanical low back pain, sports injuries, and arthritis), such agents are less effective in the treatment of neuropathic pain, including DPNP. Although some trials of high-dose opioid agonists have found adequate pain control, it is achieved at the price of a high incidence of nausea, vomiting, pruritus, and other adverse events.

Only 2 agents in the United States are approved by the FDA for treatment of DPNP: duloxetine and pregabalin. Even with the availability of these 2 agents, DPNP is often treated by combination therapy with a diversity of pharmacologic agents. Tricyclic antidepressants, serotonin-norepinephrine reuptake inhibitors (SNRIs), anticonvulsants, and mexiteline have all been studied, with the most consistent positive trial data seen for tricyclic antidepressants. Other agents that have been approved for other types of neuropathic pain, but are effective for DPNP, are gabapentin, topical lidocaine, and topiramate.

Choosing among the adjuvant analgesics can be challenging. The most recent evidence-based guidelines that focus on DPNP were developed by the ADA in 2005.12 Subsequent publications include consensus guidelines on DPNP,27 evidence-based recommendations on neuropathic pain,28 and at least one concise review of DPNP.29 Although the evidence-based recommendations are not specific to DPNP, they focus on neuropathic pain, of which DPNP is a type. In addition, they were developed by a multidisciplinary panel of pain experts, and they are the most recent evidence-based recommendations. Consequently, they serve as the basis for the following discussion.

The Dworkin evidence-based recommendations for neuropathic pain classify treatment options into 3 groups based on the strength of the results of published clinical trials and the clinical experience of the panel (TABLE 1).12,26,28,29 First- and second-line agents are supported by multiple randomized clinical trials.28 In addition to duloxetine and pregabalin, first-line agents include tricyclic antidepressants, SNRIs, calcium channel alpha2-delta ligands, and topical lidocaine. The categorization of the opioids and tramadol as second-line agents is also based on published guidelines and recommendations for their use, particularly as it relates to the potential for abuse.28 Third-line agents are categorized as such because the evidence supporting their use is limited to one positive randomized clinical trial or inconsistent results from multiple clinical trials.28 The starting doses and recommendations for titrating first- and second-line agents are provided in TABLE 2.28 Should the use of a third-line agent become necessary, consultation with a pain specialist might be considered.

The effectiveness of the majority of the first- and
second-line agents is demonstrated by the low number needed to treat (NNT) to observe a 50% reduction in pain in one patient—generally, 2 to 5.12,29 By comparison, the NNT to prevent one cardiovascular event over one year with clopidogrel vs aspirin is 196.30

In applying these recommendations for the symptomatic relief of DPNP in an individual patient, other factors are to be considered. These factors include safety, tolerability, dosage form, comorbidities, concomitant medications, cost, and other patient characteristics (TABLE 3).26,28,31-35 For example, a tricyclic antidepressant would be a good choice for a patient who is also depressed but should be avoided if the patient has heart disease. Duloxetine, pregabalin, or a tertiary amine tricyclic antidepressant would be a good choice if the patient also has a sleep disorder. For a patient with localized pain, the lidocaine patch 5% can be used, especially if comorbidities, side effects, or other issues warrant avoidance of other first-line medications. If cost is a concern, a tricyclic antidepressant would be a good choice, as they are typically the least expensive option.

Following initiation of therapy for symptomatic pain, timely monitoring is important. At each office visit, patient response and satisfaction with the treatment plan should
be assessed by asking key questions (TABLE 4).26 The use of a visual analog scale or other simple scale is helpful to monitor pain severity. A reduction in pain severity should be seen within 3 weeks of initiating therapy. If not, adherence to therapy should be investigated. In addition, patients should be questioned about factors and stressful events that might be contributing to their pain. If no mitigating circumstances are identified, the medication dosage can be increased until maximum pain reduction is achieved and/or intolerable side effects are experienced.

For many patients with chronic symptomatic DPNP, combination therapy will be required. Choosing medications based on complementary mechanisms of action is suggested to increase efficacy, decrease side effects, improve tolerability, and avoid drug interactions. Because finding the optimal regimen can be challenging, the algorithm shown in the FIGURE can be considered.12,26,28 Working collaboratively with patients—with frequent follow-up, patient education, and a willingness to modify therapy as appropriate—is important for optimal outcomes.

Summary

DPN is a common complication of T2DM that often causes a pain syndrome. The diagnosis of DPNP centers around a careful history and physical examination, aided by the use of diagnostic tools, such as the 128-Hz tuning fork. A reduction in pain severity of 30% to 50% is achievable for most patients but generally requires combination therapy. In addition to duloxetine and pregabalin, which have been approved by the FDA for DPNP, adjuvant analgesics are the mainstay of therapy. Of the adjuvant analgesics, the use of the tricyclic antidepressant and anticonvulsant groups is supported by the most extensive evidence. The selection of an adjuvant analgesic is often based on patient comorbidities and tolerability. Frequent follow-up is needed to optimize therapy.

References

The role of statins in managing diabetic dyslipidemia

Introduction

Cardiovascular disease (CVD) remains the major cause of death in patients with type 2 diabetes mellitus (T2DM). As a consequence, the prevention and treatment of CVD are critical components of comprehensive management of patients with T2DM. A major contributor to the overall cardiovascular (CV) risk in these patients is the complexity and atherogenicity of the dyslipidemia commonly observed in patients with T2DM. The focus of this article is the central role statins play in managing dyslipidemia and ultimately lowering the risk of CV events in patients with T2DM.

What is the pathophysiology of dyslipidemia in T2DM?

Although several factors are responsible for the designation of T2DM as a coronary heart disease (CHD) risk equivalent, the atherogenicity of the lipid profile is a major contributor. The pattern of mixed dyslipidemia commonly observed in patients with T2DM is a result of insulin resistance and abnormal lipid metabolism. Patients with insulin resistance have dysregulated visceral adipose tissue. Under normal circumstances, insulin inhibits the activity of hormone-sensitive lipase (HSL), an enzyme that hydrolyzes triglycerides (TGs) to free fatty acids (FFAs) and glycerol. In the setting of insulin resistance, HSL is continuously releasing FFAs from visceral adipose tissue. The FFAs are transported to the liver through the portal circulation and can be used to form TGs. These TGs are packaged into very-low-density lipoproteins (VLDL) and secreted into the circulation. This results in high serum VLDL and TG levels.

Insulin resistance also leads to the functional loss of lipoprotein lipase activity, an enzyme that catalyzes the breakdown and removal of TGs to FFAs and glycerol from TG-rich lipoproteins, chylomicrons, VLDL, and their remnants. Under these conditions, VLDL and TG levels can rise sig-
Apolipoproteins are proteins associated with lipoprotein (LDL) and high-density lipoprotein (HDL) particles. As the LDL and HDL become enriched with TGs and depleted of cholesterol ester, they become better targets for lipolysis by the enzyme hepatic lipase. Hepatic lipase converts large, buoyant LDL particles into smaller, denser, and more numerous LDL particles. These smaller particles are believed to be more atherogenic than their larger counterparts because they have a lower affinity for the LDL receptor on the surface of hepatocytes (resulting in less systemic clearance); have easier access into the subendothelial space within the vessel wall, resulting in increased lipid uptake; and are also more easily oxidized.

Oxidized LDL particles are believed to be the true substrate for macrophage scavenging, a process that produces foam cells, fatty streaks, and frank atherosclerotic plaques. As HDL is more enriched with TGs, it is catabolized and cleared by the kidney. This reduction in serum HDL is exacerbated by the fact that insulin resistance is associated with less hepatic HDL secretion. Consequently, insulin resistance is highly associated with atherogenic dyslipidemia: high VLDL and TGs, increased serum concentration of small LDL particles, and low levels of HDL. A low HDL is believed to be atherogenic because it is responsible for reverse cholesterol transport—the series of reactions by which HDL mobilizes and transports excess cholesterol and lipids from the arterial wall and back to the liver for disposal.

To account for all other atherogenic particles and better determine patient risk for CVD, measuring apolipoprotein B (Apo B) levels or calculating non–HDL-C (total cholesterol minus HDL-C) levels are recommended. Apolipoproteins are proteins associated with lipoprotein surfaces and are responsible for binding to specific receptors on cell surfaces to correctly direct lipids to target organs and body tissues involved in lipid metabolism. LDL, VLDL, and VLDL remnants all contain Apo B within their phospholipid coat. Therefore, plasma concentrations of Apo B are a measure of atherogenic lipoprotein particles and correlate with non–HDL-C. Non–HDL-C is an indirect measure of Apo B. Non–HDL-C reflects the total atherogenic lipoprotein burden in serum and, in general, is the sum of LDL-C plus VL DL-C, where VL DL-C is the TG level divided by 5. It can also be calculated by subtracting HDL-C from total cholesterol.

**What are the lipid goals for a patient with T2DM?**

The strong association between CHD and T2DM has resulted in more aggressive lipid goals from the National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP-III, based on evidence-based medicine) and the American Diabetes Association (ADA)/American College of Cardiology (ACC) Foundation (based largely on expert opinion) (TABLE 1). Each set of recommendations states that LDL-C remains the primary target goal of therapy, but these recommendations typically underestimate the atherogenic burden and the number of LDL-C particles present when TGs are elevated, particularly when exceeding 150 mg/dL, as noted in the Pravastatin or Atorvastatin Evaluation and Infection Therapy (PROVE-IT) TIMI-22 trial. In addition to LDL-C, clinicians are encouraged to determine non–HDL-C values to enhance risk prediction. In fact, studies demonstrate a stronger correlation of CVD risk with non–HDL-C, compared with LDL-C. The non–HDL-C goal is simply the LDL-C goal plus 30 mg/dL. Apo B levels have also demonstrated better predictive value over LDL-C levels.

The Apo B assay has been standardized, but it is not yet widely available. Apo B levels generally correlate with non–HDL-C levels, although some variability does exist, particularly when TGs are elevated. NCEP ATP-III has established non–HDL-C as a secondary target goal of therapy in patients with TG levels ≥200 mg/dL, independent of LDL-C, as well as an acceptable marker for Apo B in routine clinical practice. Lipid risk factors for elevated levels of non–HDL-C are elevated TGs and a low HDL-C. Low HDL-C is strongly and inversely associated with risk for CHD. Importantly, TG and HDL-C levels are not goals of therapy but, rather, a means of stratification of relative risk for CHD. ADA/ACC guidelines support the use of non–HDL-C as a predictor of CVD risk.

National Health and Nutrition Examination Survey (NHANES) 2004 data reinforced that insulin resistance is the single most important risk factor for CHD. Also, impaired fasting glucose is one of the 5 criteria for metabolic syndrome (MeTS), a special risk consideration applied to NCEP ATP III guidelines and one that is closely associated with insulin resistance. Patients with MeTS carry considerable increased risk for CHD based on highly atherogenic factors (high TGs, low HDL-C, increased small-density LDL particles), insulin resistance (and elevated insulin), impaired glucose tolerance, abdominal obesity, and elevated blood pressure. For MeTS, 3 of the 5 criteria must be met: (1) abdominal obesity (waist circumference ≥40 inches for men and ≥35 inches for
women); (2) TGs >150 mg/dL; (3) low HDL-C (<40 mg/dL for men, <50 mg/dL for women); (4) systolic blood pressure ≥130 mm Hg, diastolic blood pressure ≥85 mm Hg; (5) fasting plasma glucose >100 mg/dL. Special consideration should be given to treating these clinical features to mitigate CV risk. High-sensitivity C-reactive protein (hsCRP) has been found to correlate with components of MeTS: As the patient develops more features of MeTS, the level of hsCRP rises, and the risk for CHD increases.5

What are the recommendations to achieve these lipid goals?
Nonpharmacologic measures are an integral part of treatment for T2DM and dyslipidemia. Moderate improvements in the entire lipid profile can be expected when combining caloric reduction and increased physical activity. However, the benefits of nonpharmacologic treatment go well beyond the lipid profile, especially with conditions commonly associated with T2DM, such as hypertension and glucose impairment.

Both NCEP ATP-III and ADA/ACC recommendations include limiting saturated fat to <7% of total daily calories and dietary cholesterol to <200 mg/dL.1,2 Saturated fat is commonly found in high-fat dairy products (eg, whole milk, cheese) and fatty cuts of meat. A dose-response relationship has been demonstrated between saturated fat intake and LDL-C levels. Trans fats are also a major dietary determinant of LDL-C concentrations and should be avoided.2 Although many foods no longer contain trans fats, major sources of trans fats include products processed with partially hydrogenated oils, such as cookies, crackers, and doughnuts.

Other nonpharmacologic measures include reducing excess body weight by at least 5% to 10%, while also increasing consumption of soluble fiber and phytosterols (plant sterols and stanols). Weight loss will result in less visceral adiposity and help to relieve insulin resistance. Increased intake of soluble fiber (eg, oat bran, legumes, and apples) appears to have more benefits for CVD than does insoluble fiber (eg, cereals, breads, and pastas) because of its ability to bind bile acids in the gut and thus reduce LDL-C levels. Phytosterols and plant stanols can also significantly lower LDL-C and are widely available in a variety of sources, including fortified foods (eg, breads and margarines) and tablets. Collectively, NCEP ATP-III estimates that these lifestyle changes can reduce LDL-C levels by 20% to 30% in some individuals.2

Is a statin really the best option as initial therapy for a patient with T2DM?
To answer this question, numerous factors need to be considered, including efficacy, safety, tolerability, and cost, as well as the impact of statins on dyslipidemia and T2DM. Although nearly all landmark statin trials have enrolled subjects with T2DM, the best available evidence supporting the benefits of statins in patients with T2DM is provided by the Collaborative Atorvastatin Diabetes Study (CARDS)6 and the Heart Protection Study (HPS).7,8

### Table 1: American Diabetes Association/American College of Cardiology lipid goals for patients with type 2 diabetes mellitus

<table>
<thead>
<tr>
<th>Risk category</th>
<th>Goals</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>LDL-cholesterol (mg/dL)</strong></td>
<td><strong>Non-HDL-cholesterol (mg/dL)</strong></td>
</tr>
<tr>
<td>Highest risk</td>
<td></td>
</tr>
<tr>
<td>Known CVD, or Diabetes + ≥1 major CVD risk factor(s)</td>
<td>&lt;70</td>
</tr>
<tr>
<td>High risk</td>
<td>&lt;100</td>
</tr>
<tr>
<td>No diabetes or known clinical CVD but ≥2 major CVD risk factors, or Diabetes but no other major CVD risk factor</td>
<td></td>
</tr>
</tbody>
</table>

ApoB, apolipoprotein B; CVD, cardiovascular disease; HDL, high-density lipoprotein; LDL, low-density lipoprotein.

*Other major risk factors (beyond dyslipoproteinemia) include smoking, hypertension, and family history of premature coronary artery disease.

The specific aim of CARDS was to determine differences in vascular events and all-cause mortality between atorvastatin 10 mg/d and placebo as primary prevention in patients with T2DM and at least one CV risk factor.6 After a median follow-up of 3.9 years, atorvastatin produced mean reductions in LDL-C (40%; P<.0001) and TGs (19%; P=.0002), and a modest increase in HDL-C (1%; P<.0001).6 Markedly reduced outcomes with atorvastatin, including a 37% reduction (P=.001) in CV events, caused early termination of the trial. Atorvastatin reduced the incidence of acute CHD events 36% (95% confidence interval [CI], −55 to −9), coronary revascularization 31% (95% CI, −59 to −16), stroke 48% (95% CI, −69 to −11), and death 27% (95% CI, −48 to 1; P=.059).

Results of the HPS demonstrated similar effects with simvastatin 40 mg/d vs placebo. Analyses were performed among a total of 5963 patients with T2DM. Subgroup (eg, T2DM + CHD) analysis generally showed consistent reduction in CV events (approximately 25%).7,8 Another key finding noted in these trials was the reduction in CV events, regardless of baseline LDL-C values. In the HPS, event reduction was similar whether LDL-C was <116 or >135 mg/dL.7,8 This observation was noted in the CARDS for LDL-C levels <116 and >116 mg/dL.6 These studies suggest that baseline CV risk, and not necessarily LDL-C level, better predicts positive patient outcomes with statin therapy.

A useful tool for evaluating outcomes in statin trials is to assess the number of patients needed to treat (NNT) to prevent a CV event. The NNT has been shown to range from as low as 7 over 5.4 years in a high-risk T2DM subgroup in the Scandinavian Simvastatin Survival Study6 to 32 over 4 years in the CARDS. It is important, however, to keep in mind that the CARDS trial was terminated by the data safety monitoring board nearly 2 years early because of clear benefit with statin therapy. Had the study gone its full length of time as specified in its design, the NNT likely would have been lower. Generally, in statin trials, the NNT is inversely proportional to global CV risk. For instance, in the HPS, the NNT over 4.8 years was 18 for patients with DM + CHD/CVD, compared with 24 for those with T2DM but no CVD.8

Recent meta-analyses evaluating the efficacy of statins to reduce vascular events in primary prevention patients, including many with T2DM, have also shown consistent and robust results. Brugts et al investigated the effects of statins in patients without established CVD but with CV risk factors.10 They concluded that statin treatment was associated with a reduction in all-cause mortality (mean follow-up, 4.1 years; odds ratio [OR], 0.88), as well as reductions in major coronary and cerebrovascular events (OR, 0.70 and 0.81, respectively) among all subgroups. Similar findings were observed in a meta-analysis of statin trials by the Cholesterol Treatment Trialists’ Collaboration (CTTC).11 This study demonstrated relative-risk reductions in vascular mortality (11%), major vascular events (14%), major coronary events (16%), and stroke (10%) for every 25 mg/dL reduction in LDL-C. Additional analyses noted greater event lowering with more LDL-C reduction; and when stratified into primary and secondary prevention trials, outcome reductions were comparable.11 Another meta-analysis reported significant reductions in all-cause mortality (7%), major CV mortality (11%), and major CV events (15%) with statin therapy.12 The reported studies consistently demonstrated statin therapy reduced LDL-C levels and, subsequently, reduced vascular events among primary prevention patients with a broad range of CV risk factors, including T2DM. This suggests that statins may play a major role in preventing initial CV events in those without established CHD.

The reduction in CV events with statins is primarily attributed to their marked LDL-C-lowering ability. All statins lower LDL-C levels, but the degree of reduction varies among these agents. However, the dose of a statin that reduces LDL-C by 30% to 40% is considered optimal.3 Data from Jones et al indicates that LDL-C reduction is dose-dependent and ranges from 18% with pravastatin 10 mg/d to 55% with rosuvastatin 40 mg/d.13 Other commonly used agents, such as atorvastatin and simvastatin, have been shown to reduce LDL-C by up to 51% and 46%, respectively, at the 80 mg dose.13 Although their effects may not be as clearly defined, the improvement in other lipid parameters by statin therapy may contribute to the cardioprotection of these agents. Statins moderately increase HDL-C by 5% to 15% and reduce TGs by 7% to 30%, but these rates are highly variable and depend on baseline TG values.13-16 Similarly, lowering non–HDL-C levels with statins is also variable, but data using moderate doses of these agents have shown reductions of 24% to 40%.17

Statins have a remarkable safety profile; however, recent findings from the Justification for the Use of Statins in Prevention: an Intervention Trial Evaluating Rosuvastatin (JUPITER) sparked concern regarding the development of new-onset T2DM.18 In this study, physicians reported that newly diagnosed T2DM was significantly more common among those receiving rosvuastatin (3%)
compared with subjects receiving placebo (2.4%) \((P<.01)\). Findings from other large statin trials are conflicting.

The only study to date showing a benefit of statins on glucose parameters is the West of Scotland Coronary Prevention Study (WOSCOPS), whereas multiple other studies demonstrate a nonsignificant trend toward increasing risk for T2DM. The WOSCOPS demonstrated a 30% reduction in new-onset T2DM,19 whereas the PROVE-IT study reported a small increase.20 It is possible that this potential adverse outcome may vary among agents. A meta-analysis of major statin trials concluded that the relationship between statins and incident T2DM remains uncertain, and future trials should be designed to address this concern.20 A new agent, pitavastatin, a fully synthetic statin with a unique molecular structure, was approved in the United States in August 2009. Pitavastatin has consistently displayed neutral or beneficial effects on glucose parameters and glycemic control in patients with impaired glucose tolerance, MeTS, and T2DM.21-24 Of note, pitavastatin did not adversely affect parameters of glucose metabolism in over 20,000 patients out to 1 year.25

In addition to the statins, other lipid-altering agents are commonly used to further achieve lipid targets. These include ezetimibe, bile acid resins (ie, cholestyramine, colestipol, and colesevolam), niacin, fibrates (ie, fenofibrate, fenofibric acid, and gemfibrozil), and fish oils. Some of these agents promote LDL-C reduction; however, the effect is typically modest compared with that of statin therapy. Further, bile acid resins should be used with caution in patients with certain types of dyslipidemia, as older agents in this class can aggravate hypertriglyceridemia.26 Some of these agents are now being combined with statins to further improve lipid parameters. The impact on CV risk of adding fenofibrate therapy to ongoing statin therapy in patients with T2DM was assessed in the ACCORD trial.27 The mean baseline lipid values at time of randomization of either fenofibrate or placebo were LDL-C 100 mg/dL, triglycerides 160 mg/dL, and HDL-C 39 ml/dL. There was no difference in the primary endpoint between groups. However, consistent with other fibrate trials,26,29 there was a 31% nonsignificant trend toward risk reduction among patients with triglycerides >200 mg/dL and HDL-C <34 mg/dL. The addition of niacin therapy primarily boosts HDL-C, but also provides moderate additional reductions in TG and LDL-C levels. Treatment with ezetimibe in combination with a statin has been shown to provide incremental LDL-C reduction, compared with statin monotherapy (39% to 60%).2,20

### Are there any differences among the statins with respect to safety and tolerability?

There are subtle significant differences among the statins. Overall, each agent has an excellent safety and tolerability profile, yet not all patients can tolerate statin therapy. The primary reason for discontinuation of statin therapy is musculoskeletal effects. These adverse effects occur in approximately 10% of patients,31 are considered dose-dependent,32,33 and may vary among the statins21,32-39 (Table 2). In rare circumstances, rhabdomyolysis has been reported. The actual incidence of rhabdomyolysis with statins is difficult to quantify because of its infrequency, but data from a database of managed care claims suggest an incidence of 0.44 per 10,000 person-years when using atorvastatin, pravastatin, or simvastatin monotherapy.40 Another analysis of an administrative claims database showed incidence rates of rhabdomyolysis in hospitalized patients ranging from 1.6 to 3.5 per 10,000 person-years of use with currently available statins.41

A persistent increase in results of liver function tests (LFTs) is another possible adverse effect with statins; however, overall rates of these increases are low. Increasing serum transaminases to >3 times the upper limit of normal occurs in about 1% of patients receiving statins. The adverse effect is dose dependent, and when using maximum doses of a statin, the occurrence typically increases but is generally <3%.30 Although statins are generally regarded as safe, proper monitoring of LFTs and providing patients with education on recognizing and reporting the signs and symptoms of myotoxicity are essential.

Another potential point of difference is the effect of statins on coagulopathy when used in combination with warfarin. Several commonly used statins (eg, rosuvastatin and simvastatin) have specific language in their approved product labeling with respect to prolongation of Prothrombin Time/International Normalized Ratio (PT/INR). In a recent study by Schelleman et al, investigators observed increases in the risk of gastrointestinal (GI) bleeding in patients taking simvastatin or atorvastatin, which are metabolized significantly through the CYP450 system.42 In contrast, pravastatin, which is mainly excreted unchanged, was not associated with an increased risk of GI bleeding.

### What strategies have been used to improve outcomes of people with dyslipidemia?

Several strategies for improving patient outcomes with statins have been used. Keys to improving suboptimal
care include frequent provider communication with patients on the impact of dyslipidemia, education on achieving lipid targets, and referral for dietary counseling. Physicians’ beliefs about total cholesterol levels appear to correlate with treatment. A study assessing this association demonstrated that physicians with more aggressive management strategies used lipid-lowering agents more frequently and, subsequently, their patients had lower LDL-C values. An initiative involving Medicare recipients also resulted in an improvement in care. In this study, educational materials identifying high-risk patients who were not on statin therapy were mailed to prescribers, which resulted in significantly more patients starting statin therapy. Another successful program included implementation of action plans for patients with elevated LDL-C levels in outpatient clinics. The intervention resulted in marked reductions in LDL-C levels and greater achievement of target lipid goals. Furthermore, a strategy emphasizing physician and patient education, including completion of a 1-page assessment form, led to improved achievement of multiple CV risk markers. [To view this assessment form, please see the electronic version of this supplement at: http://www.jfponline.com/supplements.asp?id=8554.]

### Table 2

<table>
<thead>
<tr>
<th>Study</th>
<th>Treatment/placebo</th>
<th>Subjects, n</th>
<th>Rhabdomyolysis cases, n (%)</th>
<th>Myopathy cases, n (%)</th>
<th>Myalgia cases, n (%)</th>
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<tbody>
<tr>
<td>A to Z</td>
<td>Simvastatin 20 mg</td>
<td>2232</td>
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<tr>
<td></td>
<td>Simvastatin 80 mg</td>
<td>2265</td>
<td>3 (0.13)</td>
<td>6 (0.26)</td>
<td>41 (1.8)</td>
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</tr>
<tr>
<td>IDEAL</td>
<td>Simvastatin 20 mg</td>
<td>4449</td>
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<td>11 (0.25)</td>
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<td>4.8</td>
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<td>4439</td>
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<td>8901</td>
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<td>9 (0.1)</td>
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<tr>
<td>LIPS</td>
<td>Fluvastatin 80 mg</td>
<td>844</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>NR</td>
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<tr>
<td></td>
<td>Placebo</td>
<td>833</td>
<td>0 (0)</td>
<td>3 (0.4)</td>
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<td>PROVE-IT</td>
<td>Pravastatin 40 mg</td>
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<tr>
<td></td>
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<td>0 (0)</td>
<td>NR (3.3)</td>
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<td>NR*</td>
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<td>Atorvastatin 80 mg</td>
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<td>2 (0.04)</td>
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<td>241 (4.8)*</td>
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A to Z, Early Intensive versus a Delayed Conservative Simvastatin Strategy in Patients with Acute Coronary Syndromes; IDEAL, Incremental Decrease in End Points through Aggressive Lipid Lowering; JUPITER, Justification for the Use of statins in Prevention: an Intervention Trial Evaluating Rosuvastatin; LIPS, Lescol Intervention Prevention Study; NR, not reported; PROVE-IT, Pravastatin Or atorVastatin Evaluation and Infection Therapy; SEARCH, Study of the Effectiveness of Additional Reductions in Cholesterol and Homocysteine; SPARCL, Stroke Prevention by Aggressive Reduction in Cholesterol Levels; TNT, Treating to New Targets.

*Defined as discontinuation due to muscle-related adverse event.

†Occurred after trial closed.

‡Defined as muscle weakness, stiffness, or pain (but treatment/placebo not necessarily discontinued).

§Defined as discontinuation due to increased creatinine kinase or myalgias.

¶Myotoxicity broadly defined as “myopathy” with creatinine kinase >10 times the upper limit of normal.

‖Not defined.

*Defined as treatment-related myalgia.

Summary

The common lipid abnormalities associated with T2DM confer substantial CV risk. Statins are a safe and well-established treatment option for lowering this atherogenic burden and improving outcomes in this patient population. Nonetheless, many patients with T2DM are not receiving a statin, and even those who receive treatment may not be achieving recommended lipid targets. Strategies must be implemented to improve the quality of care for these patients who are at high risk for a primary or secondary CV event.
Choosing among the incretin agents and why it matters

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Dr Unger disclosed that he is on the advisory boards for Amylin Pharmaceuticals, Inc., Eli Lilly and Company, NicOx Inc., Novo Nordisk Inc., and Roche Pharmaceuticals; is on the speakers bureaus for Amylin Pharmaceuticals, Inc., Eli Lilly and Company, and Novo Nordisk Inc.; has contracted research supported by Abbott Laboratories, Amylin Pharmaceuticals, Inc., GlaxoSmithKline, Intarcia Therapeutics, Inc., Novo Nordisk Inc., Pfizer Inc, sanofi-aventis, and Takeda Pharmaceuticals North America.

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**LEARNING OBJECTIVES**

After reading this article, the primary care clinician should be better able to:

1. Describe the role of the incretin system in the pathogenesis of type 2 diabetes mellitus (T2DM)
2. Characterize the efficacy and safety of the glucagon-like peptide-1 (GLP-1) agonists and dipeptidyl peptidase-4 (DPP-4) inhibitors in combination with other glucose-lowering therapy
3. Explain the role of GLP-1 agonists and DPP-4 inhibitors in the treatment of patients with T2DM

**CASE STUDY.** ME is a 58-year-old African American male who was diagnosed with type 2 diabetes mellitus (T2DM) 3 months ago (TABLE 1). At diagnosis, his blood pressure (BP), and lipid profile were within normal limits and his eye exam was normal. He is otherwise healthy.

Lifestyle interventions and treatment with metformin were initiated at diagnosis. Dual pharmacotherapy was considered, as it is now recommended by the American Association of Clinical Endocrinologists (AACE)/American College of Endocrinology (ACE) guidelines for a patient with a glycosylated hemoglobin (A1C) level between 7.6% and 9.0%.1 However, because ME was upset with his diagnosis and overwhelmed with treatment, it was mutually decided to initiate metformin monotherapy. The dose of metformin was increased to 1000 mg twice daily (with meals) after 1 week. ME has discussed lifestyle interventions with his primary care clinician on 2 occasions. He walks for 30 minutes after lunch, 5 days per week and eats a “well-balanced diet.”

As his primary care clinician, you congratulate ME for walking after lunch during the week. You stress the importance of exercise and good nutrition, including not overeating. After ME’s graded exercise stress test is reported as normal, you encourage him to intensify his lifestyle interventions by adding resistance training to his exercise regimen.

**Introduction**

Current guidelines recommend monitoring patients every 2 to 3 months and continuing to intensify pharmacotherapy in patients who do not achieve the target A1C level of <7.0% with maximally tolerated metformin and other agents and lifestyle intervention.1,2 In this case, ME’s A1C level at 3 months is 7.9%. ME needs to continue with lifestyle interventions. But the question becomes: What agent should be added to metformin? Among the many options, the addition of a glucagon-like peptide-1 (GLP-1) agonist or dipeptidyl peptidase-4 (DPP-4) inhibitor is recom-
recomended in current guidelines. This recommendation is based on the many attributes of these agents, including their glucose-lowering effects, as well as their effects on weight, BP, and lipid profile (TABLE 2). Let’s review the data and clinical experience behind these attributes.

The discussion that follows will focus on the 4 incretin agents currently available in the United States: the GLP-1 agonists exenatide (Byetta®, Amylin Pharmaceuticals, Inc., San Diego, CA) and liraglutide (Victoza®, Novo Nordisk Inc., Princeton, NJ) and the DPP-4 inhibitors sitagliptin (Januvia®, Merck & Co., Inc., Whitehouse Station, NJ) and saxagliptin (Onglyza™, Bristol-Myers Squibb Company, Princeton, NJ). A long-acting form of exenatide is currently under review by the FDA, whereas alogliptin and vildagliptin are investigational DPP-4 inhibitors.

The role of the incretin system in glucose homeostasis

T2DM is characterized by multiple alterations in glucose homeostasis, including peripheral insulin resistance, pancreatic β-cell dysfunction, reduced insulin secretion, impaired insulin action, hyperglucagonemia, impaired fatty acid metabolism, and diminished amylin effect. Over the past 4 decades, the role of the incretin system in glucose homeostasis has been established. The insulinotropic actions of the incretin system are mediated primarily through glucose-dependent insulinotropic polypeptide (GIP) and GLP-1. In patients with T2DM, the secretion of GLP-1 is significantly impaired such that the greater the insulin resistance, the lower the rise in mealtime secretion of GLP-1. Parenteral administration of GLP-1 achieves supraphysiologic concentrations of GLP-1, leading to a dose-dependent increase in first- and second-phase insulin secretion and inhibition of postprandial glucagon secretion. The result is a reduction in fasting plasma glucose (FPG) and postprandial glucose (PPG) levels.

Rapid degradation of GLP-1 by the enzyme DPP-4 has led to the development of agents that inhibit DPP-4, thereby prolonging the action of endogenous GLP-1.

Because of the unique role played by the incretin system in glucose homeostasis and the beneficial actions of GLP-1, therapies that target this system offer the ability to complement the actions of other glucose-lowering therapies.

Glucose-lowering effects of incretins

The GLP-1 agonists and DPP-4 inhibitors lower both FPG and PPG levels, with a greater effect on PPG (TABLE 3). The importance of PPG as a therapeutic target becomes especially important as A1C levels fall to <8.5%. In addition to increasing first- and second-phase insulin secretion, the marked effect on PPG with the GLP-1 agonists may be due to slowed gastric emptying—an appetite suppression–like effect, which is seen with the pharmacologic concentrations achieved with GLP-1 agonists but not with the physiologic concentrations seen with DPP-4 inhibitors. A1C is generally reduced by 0.5% to 1.5% with the GLP-1 receptor agonists and by 0.5% to 0.8% with the DPP-4 inhibitors when used as monotherapy or when added to other glucose-lowering therapies. The glucose-lowering effect of the GLP-1 agonists and DPP-4 inhibitors has been found to be greater with a higher baseline A1C level, particularly a level >9%. Similarly, a greater reduction in A1C is observed in patients previously treated with diet and exercise alone, compared with those previously treated with another glucose-lowering agent.

Important factors to consider when initiating incretin therapy are: how long the patient has had T2DM, the baseline A1C level, and whether the patient has received previous treatment.

Non-glucose effects of incretins

Weight

Incretin-based therapies offer other benefits that are important in the management of T2DM. Body weight, for example, is an important issue, since being overweight is a major risk factor for T2DM and cardiovascular disease (CVD). Many of the current glucose-lowering therapies promote weight gain. The GLP-1 agonists promote weight loss, generally in the range of 1 to 4 kg over 6 months when used as monotherapy or in combination with other agents. Weight loss with the GLP-1 agonists is greater with increased initial body weight and is independent of the transient
nausea that is associated with their use. Instead, the weight loss associated with GLP-1 agonists likely results from their ability to promote satiety and reduce caloric intake. In contrast, the DPP-4 inhibitors generally have little, if any, impact on body weight.

**BP**

Improvement in systolic BP and lipid profile is also observed with the use of GLP-1 agonists and DPP-4 inhibitors. This effect is particularly important because of the increased risk for CVD experienced by patients with T2DM. Reduction in systolic BP has been found to be 2 to 7 mm Hg (P < .05), whereas diastolic BP generally is not significantly reduced. Although GLP-1 agonists and DPP-4 inhibitors are not appropriate for primary antihypertensive therapy, the reduction in systolic BP is beneficial.

**Lipid profile**

The lipid profile has also been observed to improve with incretin therapy. After 3.5 years of exenatide therapy, total cholesterol (P = .0007), low-density-lipoprotein cholesterol (P < .0001), and triglyceride (P = .0003) levels decreased 5%, 6%, and 12%, respectively, while high-density lipoprotein cholesterol increased 24% (P < .0001). A dose-dependent improvement in the lipid profile also has been observed with the use of DPP-4 inhibitors, with the greatest improvement in the triglyceride level (6% to 18%). One study, however, observed an increase in the triglyceride level with sitagliptin, although the increase was significantly smaller than that observed with placebo (P < .05).

**Pancreatic β-cell function and mass**

One of the attributes of the incretins is the potential to increase pancreatic β-cell function, as shown in several trials involving patients with T2DM. In a 1-year study comparing exenatide and insulin glargine, exenatide significantly improved several measures of β-cell function, including first- and second-phase glucose-stimulated C-peptide secretion and arginine-stimulated C-peptide secretion (both, P < .0001 vs glargine). Four weeks following discontinuation, β-cell function returned to pretreatment levels in both groups. Treatment with liraglutide for 14 weeks has been shown to result in similar dose-dependent improvements in first- and second-phase insulin secretion, as well as arginine-stimulated insulin secretion (all, P < .05). Other trials with liraglutide have shown significant (P = .01) improvement in β-cell function with one study showing greater improvement with liraglutide than with exenatide. However, in one monotherapy trial with liraglutide versus glimepiride, there was no significant difference in β-cell function between the 2 agents. Using the homeostasis model of assessment of β-cell function, improvement in pancreatic β-cell function has been observed with sitagliptin, saxagliptin, and vildagliptin, but not alogliptin.

If supported by long-term data, these accruing results represent an important advance in the treatment of T2DM by addressing a major pathophysiologic mechanism.

**CASE STUDY.** You consider the options recommended in the AACE/ACE 2009 guidelines for combination therapy with metformin: GLP-1 agonist, DPP-4 inhibitor, thiazolidinedione (TZD), sulfonylurea, or glinide. You recall that, with the exception of the TZDs, all of these agents have a pronounced ability to lower PPG. The durability of sulfonylureas, however, is relatively short. You note that the GLP-1 agonists promote weight loss, whereas the DPP-4 inhibitors are weight neutral, and the TZDs, sulfonylureas, and glinides promote weight gain. Given ME’s weight of 88 kg at diagnosis, the GLP-1 agonists become a good option. The ability of the GLP-1 agonists to promote satiety and reduce caloric intake is especially attractive because ME “loves to eat.” The beneficial effects of the GLP-1 agonists and DPP-4 inhibitors on BP and lipid profile are not an important consideration at this time. However, the beneficial effect of the GLP-1 agonists and DPP-4 inhibitors on pancreatic β-cell function is an important consideration because of the central role of β-cell dysfunction in the pathophysiology of T2DM. The TZDs

<table>
<thead>
<tr>
<th>TABLE 2 Glucose-lowering effects of incretins</th>
<th>GLP-1 agonist</th>
<th>DPP-4 inhibitor</th>
</tr>
</thead>
<tbody>
<tr>
<td>A1C^a</td>
<td>–0.5% to –1.5%</td>
<td>–0.4% to –0.8%</td>
</tr>
<tr>
<td>FPG</td>
<td>Mild decrease</td>
<td>Mild decrease</td>
</tr>
<tr>
<td>PPG</td>
<td>Moderate to marked decrease</td>
<td>Moderate decrease</td>
</tr>
<tr>
<td>Weight</td>
<td>Decrease</td>
<td>No change</td>
</tr>
<tr>
<td>Satiety</td>
<td>Increase</td>
<td>No change</td>
</tr>
<tr>
<td>Food intake</td>
<td>Decrease</td>
<td>No change</td>
</tr>
<tr>
<td>BP, systolic</td>
<td>Decrease</td>
<td>Decrease</td>
</tr>
<tr>
<td>Lipids</td>
<td>Improvement</td>
<td>Improvement</td>
</tr>
</tbody>
</table>

A1C, glycosylated hemoglobin; BP, blood pressure; DPP-4, dipeptidyl peptidase-4; FPG, fasting plasma glucose; GLP-1, glucagon-like peptide-1; PPG, postprandial glucose.

^aEffect with monotherapy.
also have been reported to improve β-cell function.47

Because of the advantages of the GLP-1 agonists relative to the DPP-4 inhibitors, and because the use of a GLP-1 agonist will more likely achieve an A1C level <7.0%, you tentatively determine that adding a GLP-1 agonist to ME’s treatment regimen is reasonable. However, recognizing that the GLP-1 agonists and DPP-4 inhibitors are the most recent glucose-lowering agents to become available, you now consider the safety and tolerability of these agents.

### Safety and tolerability

Hypoglycemia is an important consideration in selecting a glucose-lowering agent because of its frequent occurrence with sulfonylureas, glinides, and some insulins. Minimizing the risk and severity of hypoglycemia is especially important because of its major negative effect on morbidity, mortality, and quality of life.48 Seizures, traffic accidents, and head trauma can also occur as a result of severe hypoglycemia. Furthermore, the risk of cardiac events and death is more common in patients with hypoglycemic episodes, particularly with severe hypoglycemia,49 such that the benefit-to-risk ratio decreases progressively with the duration of T2DM.49

The incidence of hypoglycemia with the use of GLP-1 agonists and DPP-4 inhibitors is low, with no reports of severe hypoglycemia.1 In monotherapy trials, the reported incidences of minor to moderate hypoglycemia were 4% to 9% with exenatide,15,21 8% to 12% with liatriptin compared with 24% for glimepiride,16 and 6% with saxagliptin.18 The incidence of minor hypoglycemia in selected incretin monotherapy trials15-19

### Table 3

<table>
<thead>
<tr>
<th>Trial</th>
<th>Baseline</th>
<th>Change*</th>
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<tr>
<td></td>
<td>A1C (%)</td>
<td>FPG (mg/dL)</td>
<td>PPG (mg/dL)</td>
<td>A1C (%)</td>
<td>FPG (mg/dL)</td>
<td>PPG (mg/dL)</td>
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<td>Exenatide (E)/placebo¹⁴</td>
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<td>E 5 mcg bid</td>
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<td>—</td>
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<td>—18</td>
<td>—21</td>
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<td>—</td>
<td>—</td>
<td>—0.9</td>
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<td>—25</td>
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<td>L 1.2 mg bid</td>
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<td>203</td>
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<td>L 1.8 mg bid</td>
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<td>171</td>
<td>205</td>
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<td>Glimepiride 8 mg qd</td>
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<td>171</td>
<td>205</td>
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<td>Sitagliptin (S)/placebo¹⁶</td>
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<td>S 100 mg qd</td>
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<td>180</td>
<td>263</td>
<td>—0.5</td>
<td>—13</td>
<td>—41</td>
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<tr>
<td>S 200 mg qd</td>
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<td>184</td>
<td>279</td>
<td>—0.4</td>
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<td>—49</td>
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<tr>
<td>Placebo</td>
<td>8.1</td>
<td>184</td>
<td>265</td>
<td>+0.1</td>
<td>+7</td>
<td>+5</td>
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<tr>
<td>Saxagliptin (S)/placebo¹⁷</td>
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<td></td>
<td></td>
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<tr>
<td>S 2.5 mg qd</td>
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<td>156</td>
<td>—</td>
<td>—0.7</td>
<td>—11</td>
<td>—24</td>
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<tr>
<td>S 5 mg qd</td>
<td>7.9</td>
<td>169</td>
<td>—</td>
<td>—0.9</td>
<td>—22</td>
<td>—35</td>
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<tr>
<td>S 10 mg qd</td>
<td>8.0</td>
<td>169</td>
<td>—</td>
<td>—0.8</td>
<td>—16</td>
<td>—41</td>
</tr>
<tr>
<td>S 20 mg qd</td>
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<td>172</td>
<td>—</td>
<td>—0.7</td>
<td>—14</td>
<td>—28</td>
</tr>
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<td>S 40 mg qd</td>
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<td>158</td>
<td>—</td>
<td>—0.8</td>
<td>—16</td>
<td>—34</td>
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<tr>
<td>Placebo</td>
<td>8.0</td>
<td>165</td>
<td>—</td>
<td>—0.3</td>
<td>+3</td>
<td>—1</td>
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<tr>
<td>Alogliptin (A)/placebo¹⁸</td>
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<td>A 25 mg qd</td>
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<td>—</td>
<td>236</td>
<td>—0.2</td>
<td>—</td>
<td>—33</td>
</tr>
<tr>
<td>A 100 mg qd</td>
<td>7.7</td>
<td>—</td>
<td>211</td>
<td>—0.4</td>
<td>—</td>
<td>—37</td>
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<tr>
<td>A 400 mg qd</td>
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<td>—</td>
<td>254</td>
<td>—0.3</td>
<td>—</td>
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<td>—</td>
<td>231</td>
<td>+0.1</td>
<td>—</td>
<td>+8</td>
</tr>
</tbody>
</table>

A1C, glycosylated hemoglobin; FPG, fasting plasma glucose; PPG, postprandial glucose.

*As reported in the trial (may not equal baseline-treatment end due to rounding).
CHOOSING INCRETIN AGENTS

cemia with sitagliptin was 1% to 2%. One trial showed an incidence of 2% to 4% with sitagliptin, compared with 17% for glipizide.

Gastrointestinal (GI) effects, especially nausea, are important considerations when using an incretin, particularly a GLP-1 agonist. In monotherapy trials, the reported incidence rates of nausea were 3% to 13% for exenatide, 28% to 29% for liraglutide, 1% to 2% for sitagliptin, and 2% to 4% for saxagliptin. A comparison of exenatide 10 mcg twice daily with liraglutide 1.8 mg once daily showed that 28% of exenatide patients and 26% of liraglutide patients experienced nausea initially, but by 26 weeks, only 9% and 3% experienced nausea, respectively. Another liraglutide monotherapy trial observed that <10% of patients experienced nausea at the end of 4 weeks. In both the comparison and monotherapy trials, a dose escalation strategy was used to minimize the incidence and severity of nausea. Liraglutide was initiated at 0.6 mg once daily and increased by 0.6 mg a week to the maximum dose of 1.8 mg once a day. Exenatide was initiated at 5 mcg twice a day and increased to 10 mcg twice a day after 4 weeks. Glimepiride was increased from 2 mg to 4 mg to 8 mg over 2 weeks.

In addition to dose escalation, other strategies to minimize the incidence and severity of nausea include the avoidance of overeating, and minimizing the ingestion of fatty foods during the first week of therapy. It is important that the possibility of GI effects be discussed with patients prior to initiating therapy and to assure patients that most nausea resolves within a few weeks.

Of greater concern is the potential association of GLP-1 agonists with acute pancreatitis. However, because of the increased incidence of acute pancreatitis in patients with T2DM, this association is unclear. A review of data from a claims database gathered during the period 2005 to 2008 showed that the risk for acute pancreatitis in patients with T2DM treated with exenatide (n=27,996) and sitagliptin (n=16,276) was comparable to the incidence in those treated with metformin or glyburide (matched comparators) over 1 year. Seven cases of acute pancreatitis were identified in 5 clinical trials involving more than 3900 patients treated with liraglutide. In its review of the new drug application for liraglutide, the FDA noted that too few cases were observed to determine liraglutide as the cause. However, the FDA has required additional studies to better understand the risks associated with liraglutide, including pancreatitis.

It should be noted that the prescribing information for sitagliptin also describes postmarketing reports of acute pancreatitis. The FDA has directed that studies be undertaken to assess this issue. Prior to initiation of therapy with a GLP-1 agonist or DPP-4 inhibitor, patients should be screened for risk of acute pancreatitis. At initiation of therapy, patients should be informed of the risk, educated about the signs and symptoms, and given clear instructions in the event that acute pancreatitis is suspected. Periodic laboratory monitoring during therapy with a GLP-1 agonist is also advised.

Serious hypersensitivity reactions associated with sitagliptin have been described in postmarketing reports. These reactions have involved cases of anaphylaxis, angioedema, and exfoliative dermatitis. Most reactions occur within 3 months of starting therapy, although they may occur after the first dose. Drug sensitivities to a particular therapeutic agent may be difficult to determine clinically for patients taking multiple drugs. If one suspects that a DPP-4 inhibitor is responsible for causing the rash, consider stopping the drug for 2 weeks. The rash should subside quickly, usually within 7 to 10 days. Next, rechallenge the patient with the same drug. If the rash returns within 24 to 48 hours, an affirmative link between the DPP-4 agent and exfoliative dermatitis can be made. Other adverse events occurring in ≥5% patients with both sitagliptin and saxagliptin are upper respiratory tract infection and headache. Nasopharyngitis is common with sitagliptin, while urinary tract infection is common with saxagliptin.

CASE STUDY. Based on the safety profile of the GLP-1 agonists, you confirm that adding a GLP-1 agonist to metformin along with lifestyle interventions is a reasonable choice for ME. Although you determine that, other than his T2DM, ME is not at increased risk for acute pancreatitis, you discuss the possibility with him, inform him of the signs and symptoms, and advise him of the actions he should take, should it be necessary. You also discuss the need for daily injections and talk with him about his concerns. After teaching ME how to self-administer the GLP-1 agonist, he agrees to begin treatment.

References


