

# Constructing an algorithm for managing type 2 diabetes

## Focus on role of the thiazolidinediones

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### Preview

With the understanding of type 2 diabetes mellitus constantly evolving, and with the introduction of many new agents during the past few years, it is often difficult to keep up to date with the management of type 2 diabetes. This article reviews the pathophysiology of type 2 diabetes, oral pharmacologic treatment, and proposed diabetes treatment algorithms, which aim to guide clinicians in the use of thiazolidinediones (TZDs) earlier in the course of diabetes. This is important because studies indicate that sulfonylureas, biguanides, and insulin do not protect the beta cell and cannot provide sustainable glycemic control. The basis for TZD use earlier in diabetes is 2-fold: to preserve beta-cell function while maintaining appropriate glycemic control for a longer duration than is usually attained through monotherapy with a secretagogue or biguanide, and to prevent or reverse the insulin resistance phenomenon of reduced insulin utilization that appears even prior to the clinical diagnosis of diabetes. Notably, decreasing insulin resistance also may reduce the incidence of adverse atherosclerotic consequences.

■ Diabetes mellitus affects approximately 8% of American adults, and the majority of these patients develop type 2 diabetes.<sup>1,2</sup> Estimates from the third National Health and Nutrition Examination Survey in American adults indicate that approximately 19 million people have diabetes mellitus, and according to American Diabetes Association (ADA) diagnostic criteria, 29 million people have diabetes or impaired glucose tolerance.<sup>1</sup> These findings also show that approximately 47 million individuals in the United States probably have insulin resistance (ie, have the metabolic syndrome).<sup>3</sup> Furthermore, estimates of the prevalence of diabetes increased dramatically by approximately 30% from 1976 to 1980 and 1988 to 1994.

The increasing prevalence of diabetes is concerning because of the significant associated morbidity and mortality. Microvascular diseases of the eye and kidney, as well as neuropathy, can develop during the period of impaired glucose tolerance, prior to the patient being diagnosed with diabetes.<sup>4</sup> In addition, patients with type 2 diabetes have an increased incidence of cardiovascular complications. Macrovascular disease is the leading cause of death in patients with type 2 diabetes, and type 2 diabetes is considered an independent risk equivalent for developing another vascular event.<sup>5</sup>

Data from the UK Prospective Diabetes Study (UKPDS) Group recently confirmed that improved glycemic control, as measured by reductions in hemoglobin A<sub>1c</sub> (HbA<sub>1c</sub>),

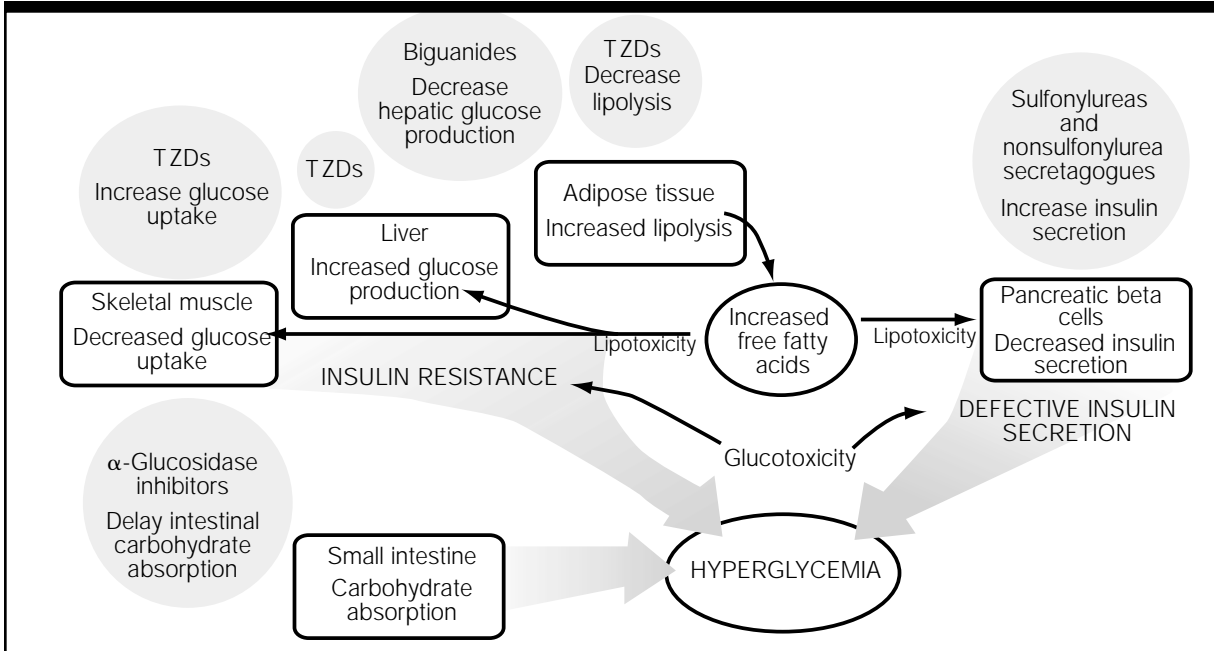


Figure 1. Pathogenesis of type 2 diabetes and targets of action for oral antidiabetic agents.

TZDs, thiazolidinediones.

Adapted and reprinted, with permission, from Inzucchi.<sup>9</sup>

reduces the incidence of microvascular complications.<sup>6,7</sup> However, the UKPDS also demonstrated that most patients with diabetes who are receiving pharmacologic therapy with sulfonylureas, biguanides, and insulin do not achieve long-lasting glycemic control. Thus, the purpose of this article is to review current treatment strategies for managing type 2 diabetes so patients can achieve prolonged glycemic control. Currently available oral pharmacologic therapies are reviewed, followed by proposed algorithms for treating patients with mild, moderate, or severe type 2 diabetes (arbitrary classifications based on fasting blood glucose levels), which can serve as an initial guide for treating non-acutely ill patients with type 2 diabetes.

## Type 2 diabetes pathogenesis and diagnosis

**PATHOGENESIS**—Normal glucose tolerance is maintained by stimulation of insulin secretion from the pancreas, suppression of endogenous hepatic glucose production, and stimulation of glucose uptake by peripheral insulin-responsive tissues (ie, muscle and fat). The latter 2 processes are mediated by insulin and are dependent on the first process, insulin release. Patients with type 2 diabetes become hyperglycemic from resistance to insulin-stimulated glucose uptake and concomitant deterioration of beta-cell function<sup>8</sup> (figure 1).

Insulin resistance is defined as the inefficient use of insulin and is a fundamental abnormality underlying the onset of type 2 diabetes.<sup>10,11</sup> Insulin resistance is often observed years

prior to the clinical diagnosis of diabetes,<sup>10</sup> and a proportion of patients with insulin resistance progress to diabetes.<sup>12</sup> Insulin resistance also has been associated with an increased incidence of cardiovascular disease.<sup>13,14</sup> Studies have shown that thiazolidinediones (TZDs) rejuvenate beta-cell activity and act as insulin sensitizers (ie, they reverse insulin resistance).<sup>15-18</sup>

**DIAGNOSIS**—The ADA created an international expert committee to develop clinical practice guidelines for the diagnosis and classification of diabetes (table 1).<sup>19</sup> The ADA recommends glycemic treatment goals as preprandial plasma glucose levels of 90-130 mg/dL, peak postprandial plasma glucose levels less than 180 mg/dL, and HbA<sub>1c</sub> levels less than 7%.<sup>19</sup> Adult, nonpregnant patients should receive

**Table 1.** Diagnostic criteria for type 2 diabetes

Any one of the following criteria confirms diagnosis of type 2 diabetes:

- Fasting plasma glucose  $\geq 126$  mg/dL (7.0 mmol/L)
- 2-hr postload 75-g glucose level  $\geq 200$  mg/dL (11.1 mmol/L)
- Random plasma glucose level  $\geq 200$  mg/dL (11.1 mmol/L) associated with symptoms (polyuria, polydipsia, weight loss)

Data from reference 19.

aggressive treatment until they reach goal levels of HbA<sub>1c</sub> less than 7%.

Recently, guidelines were published by the American Association of Clinical Endocrinologists (AACE) and the American College of Endocrinology.<sup>20</sup> The AACE guidelines are more stringent than the ADA guidelines, recommending patients be treated to HbA<sub>1c</sub> levels of less than 6.5%.

### Oral treatment of type 2 diabetes

There are 5 classes of oral antidiabetic agents (table 2), all of which have been discussed in

the preceding articles of this Special Report. Oral antidiabetic agents reduce plasma glucose levels by targeting 4 processes: (1) stimulation of pancreatic beta cells to produce more insulin (sulfonylureas, nonsulfonylurea secretagogues), (2) stimulation of glucose uptake by muscle and adipose tissues (TZDs), (3) reduction of glucose output by the liver (TZDs, biguanides), and (4) reduction of glucose absorption by the gut ( $\alpha$ -glucosidase inhibitors).<sup>35</sup> As seen in figure 1, these agents target the various pathophysiologic mechanisms of type 2 diabetes.

Nonpharmacologic therapies (ie, diet and exercise) remain the cornerstone of successful management of type 2 diabetes, even when pharmacologic agents are used.<sup>19</sup> Caloric restriction, weight loss, and exercise can enhance insulin sensitivity and glycemic control when pharmacologic therapy is being used. One of the mechanisms by which TZDs reduce hyperglycemia is by enhancing insulin sensitivity.<sup>36-39</sup>

The following section focuses on one of the newer classes of agents, the TZDs, and also gives a brief overview of the other classes. We refer the reader to other references<sup>9,35</sup> for more extensive reviews of other oral antidiabetic agents.

TZDs—Rosiglitazone and pioglitazone are the only 2 TZDs currently available in the United States.<sup>21,23</sup> Both of these agents are indicated as monotherapy in patients with type 2 diabetes or as combination therapy with a sulfonylurea,

**Table 2.** Oral antidiabetic agents and their US FDA-approved indications and uses

Class	Agent	FDA-approved indication and use
TZDs	Rosiglitazone	Monotherapy or combination with sulfonylurea, biguanide, or insulin
	Pioglitazone	Monotherapy or combination with sulfonylurea, biguanide, or insulin
Biguanides	Metformin	Monotherapy or combination with sulfonylurea or insulin
$\alpha$ -Glucosidase inhibitors	Acarbose	Monotherapy or combination with sulfonylurea, biguanide, or insulin
	Miglitol	Monotherapy or combination with sulfonylurea
Sulfonylureas (selected)	Chlorpropamide	Monotherapy
	Glipizide	Monotherapy
	Glyburide	Monotherapy or combination with biguanide or insulin
	Glimepiride	Monotherapy or combination with biguanide or insulin
Nonsulfonylurea secretagogues	Nateglinide	Monotherapy or combination with biguanide
	Repaglinide	Monotherapy or combination with biguanide or TZD

FDA, Food and Drug Administration; TZDs, thiazolidinediones.

Data from references 21-34.

**Table 3.** Oral antidiabetic agents and their US FDA-approved doses

Agent		FDA-approved dose range (daily)
<b>Thiazolidinediones</b>		
Rosiglitazone	(Avandia)	4-8 mg
Pioglitazone	(Actos)	15-45 mg
<b>Biguanides</b>		
Metformin	(Glucophage)	500-2,550 mg
<b>α-Glucosidase inhibitors</b>		
Acarbose	(Precose)	25-300 mg
Miglitol	(Glyset)	25-300 mg
<b>Sulfonylureas (selected)</b>		
Chlorpropamide	(Diabinese)	100-500 mg
Glipizide	(Glucotrol)	5-40 mg
	(Glucotrol XL)	5-20 mg (sustained release)
Glyburide	(Micronase)	1.25-20 mg
	(Glynase)	1.5-12 mg
	(DiaBeta)	1.25-20 mg
Glimepiride	(Amaryl)	1-8 mg
<b>Nonsulfonylurea secretagogues</b>		
Nateglinide	(Starlix)	180-360 mg
Repaglinide	(Prandin)	.5-16 mg

FDA, Food and Drug Administration.

Data from references 21-34.

biguanide, or insulin. (Only the 15-mg and 30-mg pioglitazone doses are approved for combination therapy,<sup>21</sup> and only the 4-mg dose of rosiglitazone is approved for use with insulin or a sulfonylurea.<sup>23</sup>) For patients who do not achieve optimal glycemic control at maximum effective (or indicated) doses of TZDs, a sulfonylurea or a biguanide may be added to the regimen. The opposite is also true: For patients who do not receive adequate glycemic control at maximum effective doses of a sulfonylurea or a biguanide, TZDs should be initiated as add-on therapy. Dose ranges of oral therapies are described in table 3.

The efficacy of TZDs in maintaining glycemic control is similar to that of sulfonylureas

and biguanides. However, sulfonylureas and biguanides do not provide durable glycemic control,<sup>6,7</sup> and only the TZDs have been shown to preserve beta-cell function.<sup>17,18</sup> Studies of long-term monotherapy and combination therapy are underway to further demonstrate the sustainability of the glycemic control achievable with TZDs.

Therapeutic benefits of using TZDs early in the treatment of type 2 diabetes include the preservation of beta-cell function, augmentation of insulin sensitivity, and minimization of hypoglycemic adverse events.<sup>15</sup> Studies suggest that the TZDs increase the responsiveness of beta cells by reducing external factors (ie, glucose and free fatty acids) that impair insulin secretion.<sup>16,40</sup> Using the homeo-

stasis model assessment method to assess insulin sensitivity and beta-cell function, treatment with rosiglitazone (8 mg/day) in patients with type 2 diabetes reduced insulin resistance by 33% and improved beta-cell function by 65%<sup>41</sup>; similar results were noted when rosiglitazone was combined with either a sulfonylurea or a biguanide.<sup>42,43</sup> Studies have also shown that treatment with TZDs significantly reduces the proinsulin-to-insulin levels, indicating improved beta-cell function.<sup>44</sup> TZDs may also exert direct effects on beta-cell recovery.<sup>17,18</sup>

Preservation of beta-cell function and improvement of insulin sensitivity are the major efficacy rationales for the use of TZDs as first-line therapy, especially because current evidence suggests that deterioration of beta-cell function and resistance to insulin begin long before the diagnosis of diabetes.<sup>36-39,45,46</sup> These data suggest that because TZDs preserve beta-cell function and improve insulin sensitivity, their use from the time of diagnosis of diabetes—or even prior to diagnosis—may improve glycemic control and prevent diabetic complications.

Rosiglitazone and pioglitazone have been proven safe and effective for long-term therapy in a number of clinical trials. TZDs are rarely associated with hypoglycemia, and severe hypoglycemia, which can occur with sulfonylureas or insulin, is no longer a contraindication to achieving glycemic targets.<sup>9</sup> Using an agent that can minimize the occurrence of this adverse event is a good way to

ensure compliance from the initiation of therapy, particularly in patients who have experienced hypoglycemic events on other therapies.

As for adverse events, TZDs may cause weight gain and edema when initiated at high doses.<sup>9</sup> The TZDs have been associated with fluid retention and have not been studied in patients with New York Heart Association class 3 or 4 cardiac status<sup>21,23</sup>; combination use with insulin may increase the incidence of cardiac failure. Troglitazone, an older TZD, was removed from the market because of idiosyncratic hepatotoxicity. Studies show that hepatic failure is not a class effect with these agents; rosiglitazone and pioglitazone have a more favorable hepatic safety profile than troglitazone.<sup>47</sup>

**BIGUANIDES**—The primary action of biguanides is to reduce production of glucose by the liver.<sup>9,26</sup> Metformin is the only biguanide available in the United States. Because the mode of action does not increase pancreatic insulin secretion, hypoglycemia is generally not associated with biguanides. However, lactic acidosis, a serious metabolic complication, has been reported with the use of metformin, particularly in individuals with renal dysfunction or advancing age.<sup>48</sup> Biguanides are indicated for monotherapy or combination therapy. They have similar efficacy to sulfonylureas and TZDs, and the most common adverse events include abdominal pain, nausea, and diarrhea, especially if taken on an empty stomach.

**α-GLUCOSIDASE INHIBITORS**—Acarbose and miglitol are α-glucosidase inhibitors that act by delaying carbohydrate absorption in the small intestine.<sup>9</sup> These agents are approved for use as monotherapy or combination therapy and are taken by patients at the beginning of each main meal.<sup>30,33</sup> The advantage of these agents is that they are essentially only minimally absorbed and are rarely associated with hypoglycemia and weight gain. However, they are less efficacious than biguanides and sulfonylureas and frequently cause flatulence, an adverse event that can be very bothersome. Because of their mechanism of action, these drugs are contraindicated in patients with diseases of the gastrointestinal tract (eg, inflammatory bowel disease).

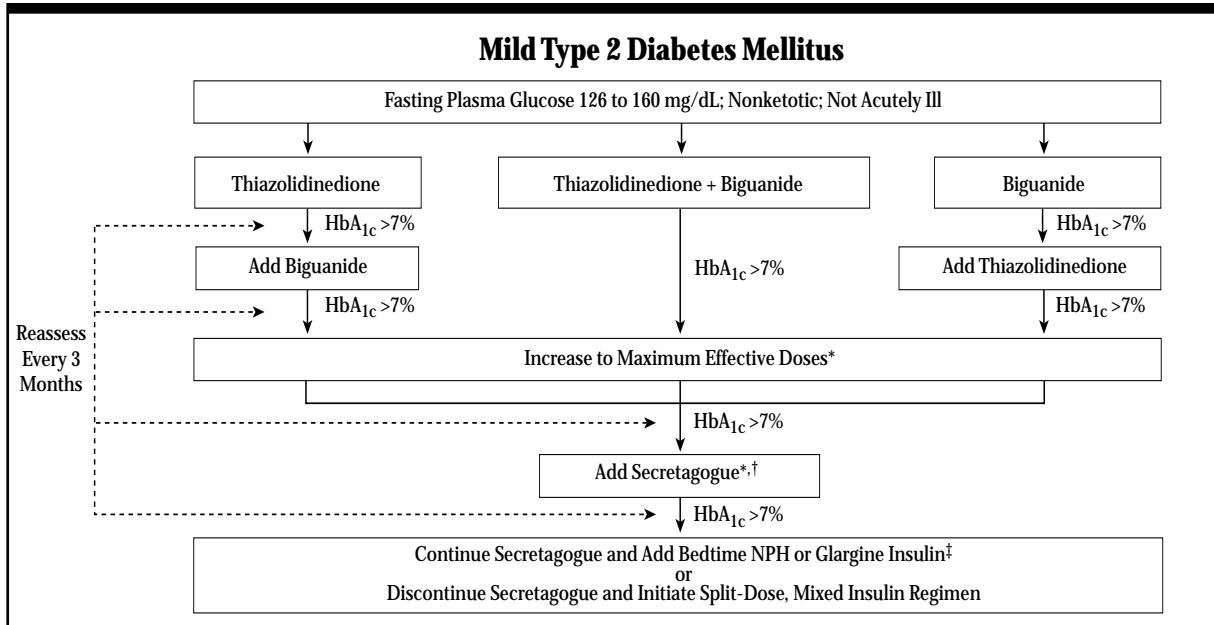
**SECRETAGOGUES**—Antidiabetic drugs that act by increasing insulin secretion are called secretagogues, and they can be separated into 2 groups: sulfonylureas and nonsulfonylurea secretagogues. Sulfonylureas are one of the oldest classes of antidiabetic agents, and there are many available. These agents are approved for use as either monotherapy or combination therapy. The 2 most common adverse events associated with sulfonylureas are hypoglycemia and weight gain. The newer or second-generation sulfonylureas (ie, glyburide, glipizide, and glimepiride) are more effective and are associated with lower incidences of adverse events than the older agents.<sup>9</sup> The nonsulfonylurea secretagogues are a newer class and include 2

currently available products: nateglinide, a phenylalanine derivative, and repaglinide, a benzoic acid derivative. Both products are approved for use as monotherapy or in combination with a biguanide. They have a shorter half-life than sulfonylureas and a reduced risk of hypoglycemia.<sup>9</sup> Because of their short half-life, resulting in shorter durations of action, the nonsulfonylurea secretagogues are administered at meals to improve postprandial glycemic control.

### **Proposed treatment algorithms for management of type 2 diabetes**

Treatment algorithms are difficult to create because therapy should ideally be individualized for each patient. However, algorithms are useful as an initial guide for management. The proposed treatment algorithms depicted in figures 2 through 4 are designed to aid the practitioner in the treatment of patients with type 2 diabetes. The algorithms are arbitrarily stratified according to fasting plasma glucose levels as mild (126 to 160 mg/dL), moderate (160 to 240 mg/dL, nonketotic, not acutely ill), and severe (240 to 350 mg/dL, nonketotic, not acutely ill) type 2 diabetes. If patients do not respond to treatment or remain acutely hyperglycemic during therapy, referral to a diabetes specialist may be appropriate.

**MILD TYPE 2 DIABETES**—Treatment of a patient with mild type 2 diabetes who presents with fasting plasma glucose levels between 126 and 160 mg/dL is depicted in figure 2. These patients are gen-



**Figure 2.** Proposed algorithm for the treatment of mild type 2 diabetes. At any point, consider referral to an endocrinologist for more intensive treatment. Biguanides are contraindicated in patients with renal disease or dysfunction (as suggested by serum creatinine levels  $\geq 1.5$  mg/dL [males],  $\geq 1.4$  mg/dL [females], or abnormal creatinine clearance), congestive heart failure requiring pharmacologic treatment, and acute or chronic metabolic acidosis. Thiazolidinediones, alone or in combination with other antidiabetic agents, can cause fluid retention, which may exacerbate or lead to heart failure.

HbA<sub>1c</sub>, hemoglobin A<sub>1c</sub>.

\* Sulfonylureas may potentiate or cause hypoglycemia and their use should therefore be reserved, whereas thiazolidinediones and biguanides, alone or in combination with each other, have rarely been shown to cause hypoglycemia.

† If hypoglycemia occurs, back-titrate or discontinue the secretagogue.

‡ Reassess in 3 months, if HbA<sub>1c</sub> > 7%, discontinue secretagogue and initiate split-dose, mixed insulin regimen.

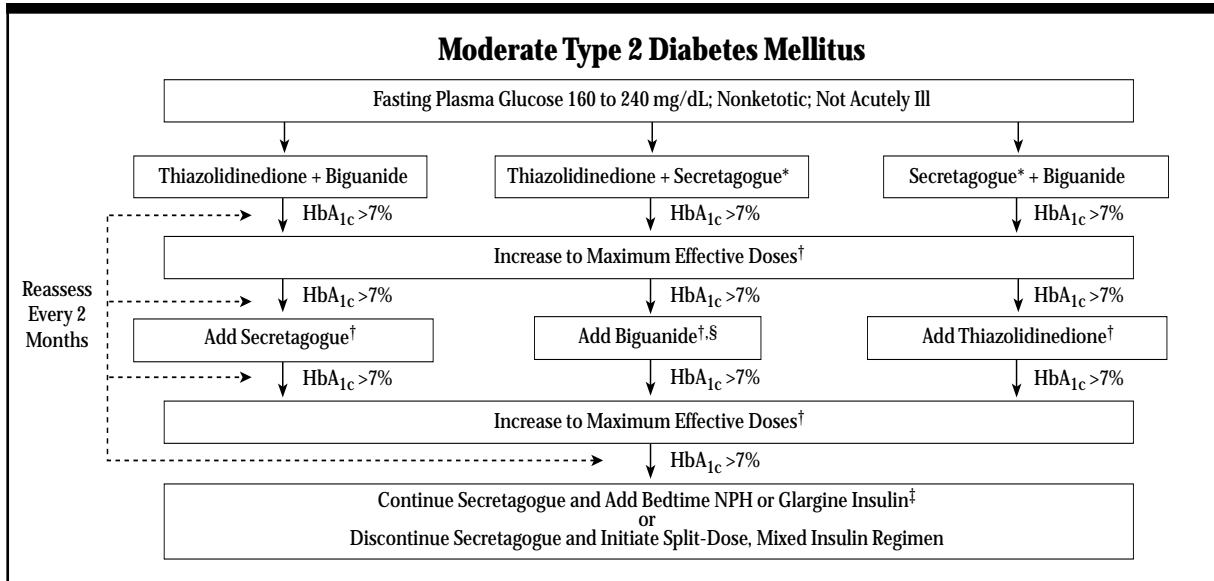
erally not acutely ill, are not ketotic, and often are asymptomatic. Patients should have their HbA<sub>1c</sub> levels measured initially and every 3 months during therapy. The goal of treatment is to reduce HbA<sub>1c</sub> levels to 7% or lower.<sup>19,20</sup>

First-line, oral therapy may include a TZD, a biguanide, or a combination of the 2. Including a TZD as part of first-line therapy is more likely to preserve the beta-cell function and improve insulin sensitivity than is inclusion of a secretagogue. If HbA<sub>1c</sub> levels remain above 7% after 3 months of monotherapy, then combination therapy may be initiated. Combination therapy with a TZD and a

biguanide offers the additional benefit of complementary mechanisms of action. If the response is still suboptimal after initiating combination therapy, the TZD and biguanide should be titrated to maximal effective doses to achieve glycemic targets.

The logic behind reserving secretagogues for second- or third-line therapy is that these agents do not treat the underlying insulin resistance. Indeed, the secretagogues, by the nature of their action, force additional insulin to be secreted by beta cells, which are already unable to produce sufficient insulin and are to some extent functionally compromised. It is un-

likely that beta-cell function is prolonged with such an approach. Another important benefit of delaying secretagogue therapy is that combining a TZD and a biguanide does not cause hypoglycemia, in contrast to sulfonylurea or insulin therapy, which may potentiate or cause hypoglycemia. However, if combination TZD-biguanide therapy at maximum effective doses does not reduce HbA<sub>1c</sub> levels to below 7%, then the addition of a low-dose secretagogue is justified. If hypoglycemia occurs, the sulfonylurea should be back-titrated or discontinued. After an adequate amount of time, if the patient does not respond to oral triple



**Figure 3.** Proposed algorithm for the treatment of moderate type 2 diabetes. At any point, consider referral to an endocrinologist for more intensive treatment. Biguanides are contraindicated in patients with renal disease or dysfunction (as suggested by serum creatinine levels  $\geq 1.5$  mg/dL [males],  $\geq 1.4$  mg/dL [females], or abnormal creatinine clearance), congestive heart failure requiring pharmacologic treatment, and acute or chronic metabolic acidosis. Thiazolidinediones, alone or in combination with other antidiabetic agents, can cause fluid retention, which may exacerbate or lead to heart failure.

HbA<sub>1c</sub>, hemoglobin A<sub>1c</sub>.

\* Sulfonylureas may potentiate or cause hypoglycemia and their use should therefore be reserved, whereas thiazolidinediones and biguanides, alone or in combination with each other, have rarely been shown to cause hypoglycemia.

† If hypoglycemia occurs, back-titrate or discontinue the secretagogue.

‡ Reassess in 3 months, if HbA<sub>1c</sub> > 7%, discontinue secretagogue and initiate split-dose, mixed insulin regimen.

§ If biguanide is contraindicated, add basal insulin, taper off secretagogue, and introduce bolus insulin as needed.

therapy, an insulin regimen may be initiated and the TZD-biguanide therapy continued. The secretagogue may be continued if bedtime NPH or glargine insulin is added, or the secretagogue can be discontinued and a split-dose, mixed insulin regimen initiated.

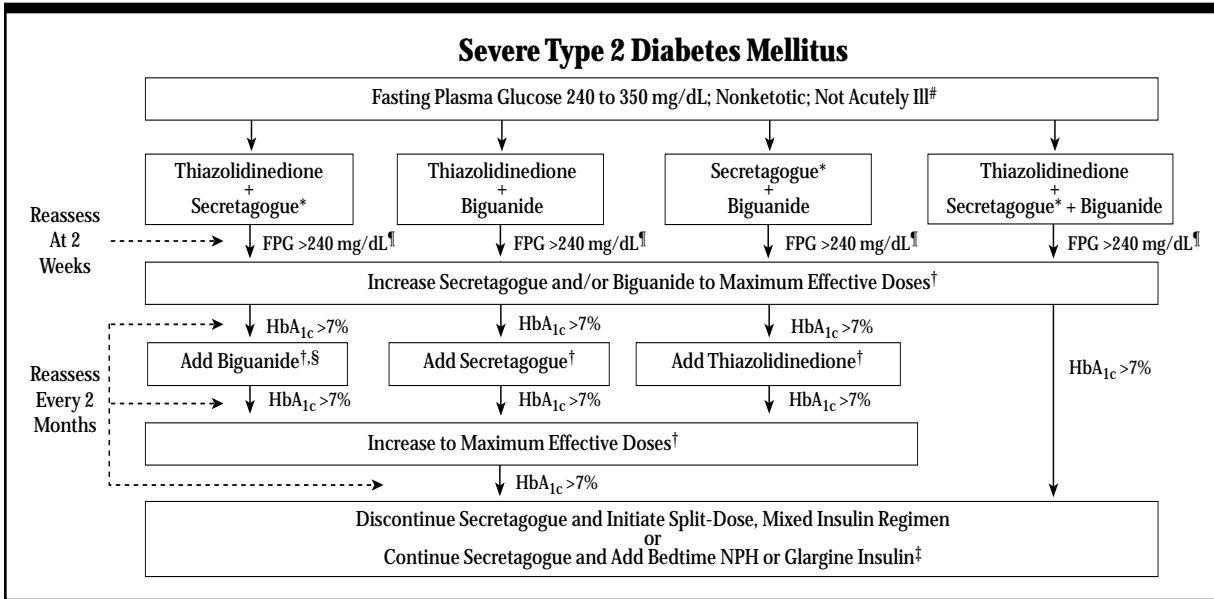
**MODERATE TYPE 2 DIABETES**—Patients with moderate type 2 diabetes (fasting plasma glucose levels between 160 and 240 mg/dL) who are not acutely ill and are nonketotic should be treated according to the algorithm depicted in figure 3. These patients should have HbA<sub>1c</sub> levels monitored every 2 months until they reach the goal of less than 7%.

As described in this algo-

rithm, initial therapy with 2 agents is warranted. Acceptable combination regimens include a TZD with a biguanide or a secretagogue. Notably, TZDs may not exert an effect on HbA<sub>1c</sub> immediately; therefore, failure to see a response within the first few weeks should not result in their discontinuation. If possible, sulfonylurea therapy should be avoided as initial therapy because it can potentiate or cause hypoglycemia, especially when used in combination with other agents. In addition, secretagogues have no influence on reducing insulin resistance. Doses of both agents may be increased until the HbA<sub>1c</sub> level is less than 7%, provided the maximum effec-

tive dose is not exceeded. If this therapy continues to be suboptimal, a third agent may be added so that the regimen includes a TZD, secretagogue, and biguanide. If the glycemic targets are not reached on triple oral therapy, bedtime NPH or glargine insulin may be added, or the secretagogue may be replaced with a split-dose, mixed insulin regimen.

**SEVERE TYPE 2 DIABETES**—Patients with severe type 2 diabetes (fasting plasma glucose levels between 240 and 350 mg/dL) who are not acutely ill and are not ketotic may be treated initially with double or triple therapy (figure 4). These patients should be monitored more closely than pa-



**Figure 4.** Proposed algorithm for the treatment of severe type 2 diabetes. At any point, consider referral to an endocrinologist for more intensive treatment. Biguanides are contraindicated in patients with renal disease or dysfunction (as suggested by serum creatinine levels  $\geq 1.5$  mg/dL [males],  $\geq 1.4$  mg/dL [females], or abnormal creatinine clearance), congestive heart failure requiring pharmacologic treatment, and acute or chronic metabolic acidosis. Thiazolidinediones, alone or in combination with other antidiabetic agents, can cause fluid retention, which may exacerbate or lead to heart failure.

FPG, fasting plasma glucose; HbA<sub>1c</sub>, hemoglobin A<sub>1c</sub>.

\* Sulfonylureas may potentiate or cause hypoglycemia and their use should therefore be reserved, whereas thiazolidinediones and biguanides, alone or in combination with each other, have rarely been shown to cause hypoglycemia.

† If hypoglycemia occurs, back-titrate or discontinue the secretagogue.

‡ Reassess in 3 months, if HbA<sub>1c</sub> > 7%, discontinue secretagogue and initiate split-dose, mixed insulin regimen.

§ If biguanide is contraindicated, add basal insulin, taper off secretagogue, and introduce bolus insulin as needed.

# If at any time the patient is symptomatic or acutely ill, consider aggressive, empiric insulin therapy with appropriate guidance.

¶ For patients who remain symptomatic, consider initiating split-dose, mixed insulin regimen and discontinuing secretagogue (if on a secretagogue) or adding bedtime NPH or glargine insulin and continuing secretagogue (if on a secretagogue).

tients with moderate type 2 diabetes, and fasting plasma glucose levels should be measured every 2 weeks until the patient is asymptomatic. In patients with severe type 2 diabetes, insulin may be useful initially to lessen not only symptoms, but also the effects of glucotoxicity on insulin resistance and insulin release from the beta cells.

At maximum effective doses of triple therapy with a TZD, secretagogue, and biguanide, insulin may be substituted for the secretagogue if the fasting plasma glucose level remains elevated or if the patient is

symptomatic. Because of the urgency to reduce such high glucose levels that could lead to the dangerous consequences from continued hyperglycemia, it may be recommended that further management be conducted by a specialist.

### Conclusions

A treatment regimen for type 2 diabetes that does not include an agent to improve insulin resistance and preserve beta-cell function is incomplete. The proposed algorithms in this article recommend the early use of TZDs to improve beta-cell function and insulin

sensitivity from the onset of therapy. First-line, oral therapy for mild type 2 diabetes should include a TZD or a biguanide as monotherapy or both agents as combination therapy. For moderate type 2 diabetes, initial therapy may consist of a TZD in combination with a biguanide or a secretagogue. Patients with severe type 2 diabetes should be more closely monitored and may require triple therapy with a TZD, secretagogue, and biguanide from the onset. Insulin may be needed if a patient does not attain glycemic goals on triple oral therapy.

In conclusion, TZDs are an excellent option for the first-line treatment of type 2 diabetes, either alone or in combination with other agents. The early use of TZDs may preserve the integrity of the beta cell and does improve

insulin sensitivity, the underlying pathologic defects associated with type 2 diabetes. Appropriate management of patients with type 2 diabetes mellitus slows the progression of disease, reduces the development of diabetic complications,

and improves clinical outcomes. The proposed algorithms discussed in this article should serve as an initial guide to practitioners who treat patients with type 2 diabetes. ■

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