

**HAROLD E. LEBOVITZ, MD***

Professor of Medicine, Division of Endocrinology and
Metabolism/Diabetes, State University of New York
(SUNY) Health Sciences Center, Brooklyn

Treating hyperglycemia in type 2 diabetes: New goals and strategies

■ ABSTRACT

To achieve glycemic goals in type 2 diabetes, one must usually use combinations of oral agents or oral agents plus insulin. This paper discusses the metabolic derangements of type 2 diabetes, the different classes of antihyperglycemic drugs, and strategies for using these drugs rationally.

■ KEY POINTS

The American Diabetes Association calls for a goal hemoglobin A_{1c} level of 7.0% in type 2 diabetes; other organizations set the goal at 6.5%. Plasma glucose levels that correspond to a hemoglobin A_{1c} level of 6.5% are a fasting level less than 110 mg/dL and a 2-hour postprandial level less than 140 mg/dL.

Both fasting and postprandial glucose levels need to be monitored and controlled, as do components of the metabolic syndrome such as insulin resistance, dyslipidemia, hypertension, and a procoagulant state.

Agents that decrease fasting plasma glucose levels selectively (eg, sulfonylureas and metformin) or in conjunction with lowering postprandial glucose excursions (eg, repaglinide, pioglitazone, and rosiglitazone) lower mean hemoglobin A_{1c} levels 1.5 to 2.0 percentage points.

Agents that primarily lower postprandial hyperglycemia are the alpha-glucosidase inhibitors and nateglinide. These decrease mean hemoglobin A_{1c} levels by 0.5 to 1.0 percentage points.

WE ARE TAKING type 2 diabetes mellitus a lot more seriously than in the past, and treating it more aggressively.

For starters, forget about the old term for the disease, “non–insulin-dependent diabetes.” Many patients with type 2 or adult-onset diabetes *do* need insulin. In fact, some need basal insulin treatment with intermediate-acting or long-acting insulins, while a few may need pre-meal insulin treatment to control postprandial hyperglycemia in addition to basal treatment.

We now have a menu of oral antihyperglycemic drugs and new insulin preparations that, if used rationally, can greatly improve metabolic control and decrease complications in most patients.

This review provides a practical perspective on how to use the new drugs, discussing how they work, their effect on components of the metabolic syndrome, their adverse effects, and how they can be used in combination.

■ CONSEQUENCES OF TYPE 2 DIABETES

Type 2 diabetes is one of the major problems confronting the health care system. By 2010, its prevalence will have increased approximately 2.5-fold from 1990 figures.¹ It is the leading cause of new blindness² and end-stage renal disease,³ it accounts for slightly more than one half of lower-extremity amputations,⁴ and it is a major risk factor for cardiovascular disease.⁵

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TABLE 1

Antihyperglycemic drugs for type 2 diabetes

| DRUG | DOSE | MECHANISM OF ACTION |
|-------------------------------------|----------------------------|---|
| Insulin secretagogues | | |
| Sulfonylureas | (one or two divided doses) | Close K_{ATP} channel and open Ca^{2+} channel of beta cells |
| Glipizide | 2.5–25 mg/day* | |
| Glipizide GITS | 2.5–10 mg/day* | |
| Glyburide | 1.25–15 mg/day* | |
| Micronized form | 1–12 mg/day | |
| Glimepiride | 1–8 mg/day | Close K_{ATP} channel and open Ca^{2+} channel of beta cells |
| Rapid-acting | | |
| Nateglinide | 60–120 mg with each meal | |
| Repaglinide | 0.5–4.0 mg with each meal | Decrease hepatic glucose production Increase glucose uptake Decrease lipolysis |
| Basal insulins | Highly variable | |
| NPH | | |
| Lente | | |
| Ultralente | | |
| Glargine | | Increase postprandial glucose uptake |
| Pre-meal insulins | Highly variable | |
| Regular | | |
| Lispro | | |
| Aspart | | Increases insulin action in liver Decreases hepatic gluconeogenesis |
| Insulin sensitizers | | |
| Biguanide | | |
| Metformin | 500–1,000 mg twice daily | Increase insulin-mediated glucose uptake in muscles and adipose tissue Increase adipogenesis |
| Thiazolidinediones | | |
| Pioglitazone | 15–45 mg/day | |
| Rosiglitazone | 4–8 mg/day | Inhibit cleavage of oligosaccharides in intestine |
| Alpha-glucosidase inhibitors | | |
| Acarbose | 25–100 mg with each meal | |
| Miglitol | 50–100 mg with each meal | |

*These are the dose ranges that have been shown to be effective in the clinic. The manufacturers recommend higher ranges: glipizide to 40 mg/day; glipizide GITS to 20 mg/day; glyburide to 20 mg/day.

Insulin secretagogues work only if enough beta cells remain

WHAT GOES WRONG

Beta cell dysfunction

In type 2 diabetes, the normal physiologic relationship between plasma glucose levels and insulin secretion is impaired, due to disturbances in pancreatic beta cell function. These disturbances express themselves clinically in three major ways:

- The normal increase in insulin secretion that occurs after eating is delayed,⁶ resulting in early, exaggerated postprandial hyperglycemia and, potentially, late postprandial hypoglycemia.⁷

- Not enough insulin is secreted to meet the needs of insulin-sensitive tissues.⁸
- The insulin-secreting function of beta cells progressively declines.⁹

Insofar as possible, treatment strategies need to address all of these issues.

Insulin resistance

Most patients who develop type 2 diabetes have insulin resistance, which precedes and probably promotes the progression from normal glucose tolerance to impaired glucose tolerance and then to type 2 diabetes.^{10,11}

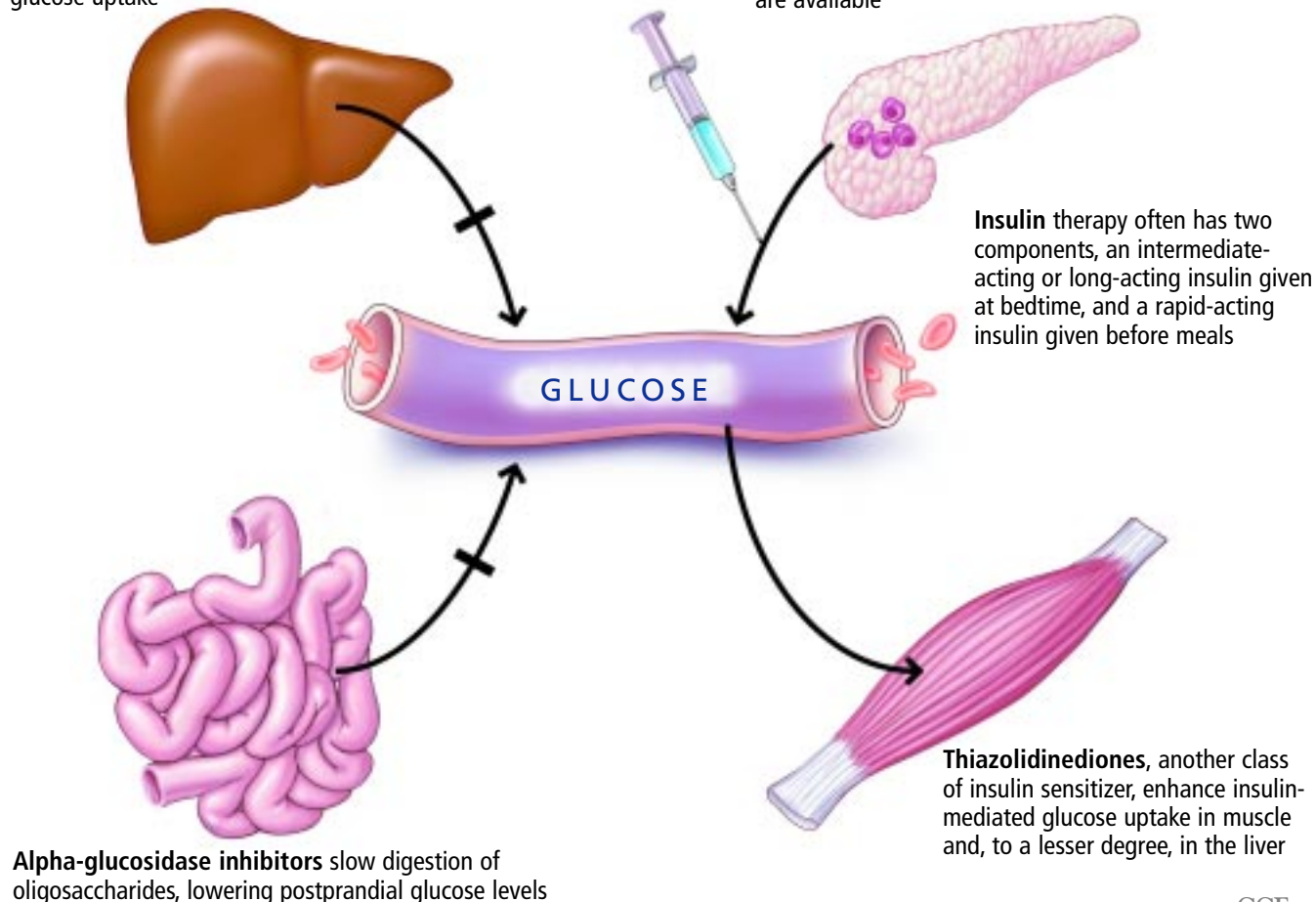
The pancreas tries to compensate for

■ Drug therapy for type 2 diabetes

Drug therapy for type 2 diabetes aims to control blood sugar levels both in the basal (fasting) state and postprandially; rational combinations of agents with different mechanisms of action can be used

Metformin, an insulin sensitizer, increases insulin action in the liver, lowering glucose production and fasting glucose levels. It may have a small effect in increasing insulin-mediated muscle glucose uptake

Insulin secretagogues close ATP-sensitive potassium channels in the beta cells of the pancreas, increasing insulin production; slow-acting and rapid-acting agents are available



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FIGURE 1

insulin resistance by secreting more insulin,⁸ but patients with the genetic predisposition to develop type 2 diabetes cannot secrete enough.

In addition, insulin resistance either causes or is associated with a cluster of metabolic abnormalities known as the *insulin resistance syndrome*, the *metabolic syndrome*, or the *dysmetabolic syndrome*.^{10,12} The components of this syndrome—eg, glucose intolerance, dyslipidemia, hypertension, a procoagulant state, and a noninfective inflammatory state—are cardiovascular risk factors, and patients with the syndrome have a higher risk of cardiovascular diseases.^{13,14}

The third Adult Treatment Panel (ATP III)¹⁵ of the National Cholesterol Education Program has provided clinical criteria for diagnosing the metabolic syndrome. A patient can be considered to have the metabolic syndrome if he or she has any three of the following five criteria :

- Increased waist circumference (> 40 inches in men; > 35 inches in women)
- Plasma triglycerides ≥ 150 mg/dL
- Plasma high-density lipoprotein (HDL) cholesterol < 40 mg/dL (men) or < 50 mg/dL (women)
- Blood pressure $\geq 130/85$ mm Hg
- Fasting plasma glucose ≥ 110 mg/dL.

TABLE 2

Sulfonylureas vs rapid-acting insulin secretagogues (nateglinide and repaglinide)

| | SULFONYLUREAS | RAPID-ACTING SECRETOGOGUES |
|--|----------------------|----------------------------|
| Early meal-mediated insulin secretion | No effect | Increase |
| Late meal-mediated insulin secretion | Marked increase | Increase |
| Early meal-mediated hyperglycemia | Slight effect | Decrease |
| Late meal-mediated hyperglycemia | Marked decrease | Decrease |
| Fasting hypoglycemia | Moderate occurrence | Small occurrence |
| Weight gain | Moderate | Small |
| Effect on K_{ATP} channels in myocardium and coronary arteries | Possible | None |
| Dosing | Once or twice daily | With each meal |
| Approximate cost | \$7.50–\$26.00/month | \$75.00–\$85.00/month |

Sulfonylureas decrease late but not early postprandial hyperglycemia

Treatment strategies for type 2 diabetes must target insulin resistance, as improvement in insulin action allows endogenous insulin to be more effective and reduces cardiovascular risk factors.

■ GLUCOSE METABOLISM: FASTING AND POSTPRANDIAL

During fasting, glucose and insulin levels decline. The liver responds to low insulin levels by producing glucose in a process called *gluconeogenesis*, which plays the major role in controlling fasting plasma glucose levels.^{16,17} In contrast, postprandial glucose levels are regulated largely by uptake by muscle cells.^{16,17}

The insulin level necessary to turn off glucose production in the liver is significantly lower than the level necessary to drive glucose into muscle cells. Therefore, patients with type 2 diabetes have a dissociation between the regulation of fasting and postprandial hyperglycemia—specifically, they can have normal or even low fasting glucose levels but still have large excursions after meals. Continuous monitoring over 48 to 72 hours has confirmed that patients with type 2 diabetes cannot achieve target glycemic control unless both fasting and postprandial glucose levels are measured, and unless treatments are given to appropriately regulate each.

■ ANTIHYPERGLYCEMIC AGENTS

Diet and exercise are the first step of therapy for type 2 diabetes; if these do not keep blood sugar at goal levels, then antihyperglycemic agents are added.

Four major classes of antihyperglycemics can be used (TABLE 1, FIGURE 1), either as monotherapy or, more appropriately, in combination with one another:

- Insulin secretagogues
- Insulins
- Insulin sensitizers
- Alpha-glucosidase inhibitors.

■ INSULIN SECRETOGOGUES

Insulin secretagogues correct hyperglycemia by stimulating insulin secretion—but only if the patient still has enough functioning beta cells.

The mechanism uses the same final pathway as glucose itself.^{7,18} When plasma glucose levels rise, potassium channels in the plasma membrane of beta cells normally close; these channels are sensitive to intracellular adenosine triphosphate levels and so are designated K_{ATP} . Closure of K_{ATP} channels causes adjacent calcium channels to open. The resultant increase in cytosolic calcium stimulates insulin granule secretion. In type 2 diabetes, the signal is deficient and delayed.

**TABLE 3****Characteristics of insulin preparations and insulin analogues**

| PREPARATION | ONSET (HOURS) | PEAK (HOURS) | EFFECTIVE DURATION (HOURS) |
|------------------------------|---------------|-------------------|----------------------------|
| Rapid-acting | | | |
| Lispro (analogue) | 0.25 | 1 | 3 |
| Aspart (analogue) | 0.25* | 1* | 3–4* |
| Short-acting | | | |
| Regular (soluble) | 0.5–1.0 | 2–3 | 3–6 |
| Intermediate-acting | | | |
| NPH (isophane) | 2–4 | 7–8 | 10–12 |
| Lente (zinc suspension) | 2–4 | 7–8 | 10–12 |
| Long-acting | | | |
| Ultralente (zinc suspension) | 4 | Variable | 18–20 |
| Glargine (analogue) | 1–2 | Flat, predictable | 24* |

*Occasionally less

Insulin secretagogues close K_{ATP} channels by binding to specific receptors on these channels. Thus, they can supplement an insufficient response to glucose. On the other hand, they have no primary effect on the components of the metabolic syndrome.

The major side effects of insulin secretagogues (and insulin replacement) are hypoglycemia and weight gain.

Sulfonylureas

Sulfonylurea drugs—eg, glipizide (Glucotrol), glyburide (Diabeta, Micronase), glimepiride (Amaryl)—increase the quantity of insulin secreted in patients with type 2 diabetes, but do not correct the delay in meal-mediated insulin secretion because their binding to receptors on the K_{ATP} channel is slow and prolonged.^{19–21} Thus, they decrease late but not early postprandial hyperglycemia.^{19–21} In fact, in the early stages of type 2 diabetes, sulfonylurea therapy often leads to late postprandial hypoglycemia because of a marked increase in late meal-mediated insulin secretion.

Rapid-acting secretagogues

Two other available insulin secretagogues also work by binding to and closing K_{ATP} channels, but they bind and detach more rapidly

than the sulfonylureas and have a shorter plasma half-life. Thus, they have a faster onset and shorter duration of action.^{22–25}

Nateglinide (Starlix) binds to the same site as the sulfonylureas. Given either with or shortly before a meal, it rapidly increases meal-mediated insulin secretion, and this effect lasts 3 to 4 hours.²⁶ Its primary effect is to reduce postprandial hyperglycemia.²⁷

Repaglinide (Prandin) binds to a different site on the K_{ATP} channel, and its binding is slightly slower and more prolonged than that of nateglinide.^{28,29} It greatly reduces postprandial hyperglycemia, but because its effects are more prolonged, it also greatly reduces fasting hyperglycemia.³⁰

Relative advantages and disadvantages

The rapid-acting insulin secretagogues, given three times a day with meals, restore normal postprandial glucose metabolism more closely than do the sulfonylureas, which are given once or twice daily (TABLE 2). Moreover, unlike the sulfonylureas, they interact little or not at all with K_{ATP} channels in cardiovascular tissues. (There has been some concern, though still controversial, that causing closure of K_{ATP} channels in the myocardium and coronary arteries might interfere with some protection against acute ischemia.)

Nateglinide and repaglinide will not work if a sulfonylurea did not

Both types of insulin secretagogues act by closing K_{ATP} channels; therefore, combining a sulfonylurea with a rapid-acting insulin secretagogue is likely to be of no benefit. Moreover, rapid-acting insulin secretagogues will not work in patients in whom sulfonylureas do not work.

■ INSULINS: BASAL AND BOLUS

As beta cell function deteriorates during the course of type 2 diabetes, insulin secretagogues eventually become ineffective.^{4,31} At that stage, the patient needs insulin replacement (TABLE 3).

Basal insulin replacement

An early sign that the beta cells are becoming less responsive to insulin secretagogues is that fasting plasma glucose levels begin to rise. The reason: so much insulin is depleted during meals that little or none is left for secretion overnight to control hepatic glucose production.

This can be managed by giving neutral protamine Hagedorn (NPH) or Lente insulin at bedtime (10 to 11 PM).^{32,33} Giving the dose at bedtime provides circulating insulin from 1 to 8 AM and can be used to regulate plasma glucose levels overnight.³⁴ The dose is adjusted every 3 or 4 days until the fasting plasma glucose level is 110 to 120 mg/dL.³³

The absorption and effects of NPH and Lente insulins vary substantially from day to day, however. A better option may be insulin glargine (Lantus), which has less variability in its action and a longer duration of action. It can be given at 6 PM or bedtime to achieve overnight glycemic control.³⁵

At this stage, most patients should continue to take an oral agent in the daytime along with insulin at night.^{33,35}

Rapid-acting insulins

As beta cell function deteriorates further, the patient may need both a basal insulin to control fasting blood sugar levels and boluses of a rapid-acting insulin to cover postprandial levels.³⁶ This goal can be best achieved by giving a long-acting insulin such as insulin glargine in the evening and a rapid-acting insulin such as insulin lispro (Humalog) or insulin aspart

(NovoLog) before each meal (TABLE 3).³⁷

If a patient needs a less-intensive regimen, for whatever reason, the regimen most often used is a mixture of a short-acting and an intermediate-acting insulin, given twice a day, ie, before breakfast and before the evening meal.³⁸ Several premixed formulations are available.

■ INSULIN SENSITIZERS

Two classes of insulin sensitizers are currently available. They increase insulin sensitivity by different mechanisms and have their primary effects in different tissues.

Metformin, a biguanide

Metformin (Glucophage), a biguanide, has been used to treat type 2 diabetes for more than 40 years.

Metformin's mechanism of action is still unknown, despite extensive studies. Its primary effect on glucose metabolism is to decrease the exaggerated hepatic glucose production that causes fasting hyperglycemia.³⁹ It does so by increasing insulin action in the liver, thereby reducing hepatic gluconeogenesis.⁴⁰

Whether metformin affects glucose uptake in the muscles and other peripheral tissues is controversial. Earlier studies^{41,42} showed modest increases in whole-body insulin-mediated glucose uptake, but they did not control for weight loss and improvement in glycemia. Later studies that controlled for these confounding factors showed little or no effect.^{43,44}

Clinically, metformin decreases plasma insulin levels, causes a small amount of weight loss, and improves some of the components of the insulin resistance syndrome (TABLE 4).^{45,46} It lowers fasting hyperglycemia but has little or no effect on postprandial hyperglycemia.⁴⁵

Metformin may even reduce the incidence of coronary artery disease. Overweight patients with type 2 diabetes who received metformin in the United Kingdom Prospective Diabetes Study (UKPDS)⁴⁷ had a 39% lower incidence of myocardial infarction and a 42% lower incidence of diabetes-related deaths compared with patients undergoing conventional treatment (ie, lifestyle modifica-

Adjust the bedtime insulin dose every 3 or 4 days until the fasting glucose is 110 – 120

**TABLE 4****Effects of insulin sensitizers**

| EFFECT | METFORMIN | THIAZOLIDINEDIONES |
|----------------------------|------------------------------|---|
| Insulin sensitivity—liver | Significant increase | Small increase |
| Insulin sensitivity—muscle | Controversial | 25% to 40% increase |
| Hyperinsulinemia | Small decrease | Decrease |
| Plasma free fatty acids | Small decrease | 25% reduction |
| Dyslipidemia* | Minimal effect | Significant improvement |
| Procoagulant state | Decreased PAI-1 [†] | Decreased PAI-1 |
| Hypertension | No effect | 2–4 mm Hg reduction in diastolic blood pressure |
| Visceral adiposity | Some decrease | No effect |
| Body weight | Decrease or no change | Weight gain of 2–3 kg |
| Endothelial dysfunction | Improved | Improved |
| Edema | None | 4% to 5% incidence |
| Urinary albumin excretion | No primary effect | Glycemia-independent reduction |

*Dyslipidemia consists of increased plasma triglycerides, decreased plasma high-density lipoprotein cholesterol, and a shift in low-density lipoprotein cholesterol particle size from large and buoyant to small and atherogenic. Thiazolidinediones reverse these abnormalities.

[†]Plasminogen activator inhibitor-1

tion). These differences were highly statistically significant and did not occur in overweight patients treated with insulin or sulfonylureas, although the improvement in glycemic control was similar.

Metformin contraindications. Metformin is contraindicated in patients with impaired renal function (serum creatinine ≥ 1.5 mg/dL in men, ≥ 1.4 in women; or creatinine clearance < 60 mL/minute), symptomatic congestive heart failure being treated by drugs, or confirmed acidosis. These all predispose to metformin-induced lactic acidosis, which, however, is rare in the absence of these factors.^{46,48}

Since radiographic contrast material can occasionally cause impaired renal function, metformin should be stopped at the time of such studies and restarted when it is clear that renal function has not been compromised.

Metformin side effects. The major problems with metformin treatment are abdominal discomfort and diarrhea. These are dose-related and preclude full dosing in 10% to 20% of patients. Giving metformin with meals and

titrating the dose from 0.5 g/day up to 2.0 g/day over a week or so decreases the severity of gastrointestinal side effects. The slow-release form of metformin seems to cause fewer gastrointestinal side effects.

Thiazolidinediones

The thiazolidinediones pioglitazone (Actos) and rosiglitazone (Avandia) decrease peripheral insulin resistance by enhancing insulin-mediated glucose uptake by muscle.^{12,49–51} They have a lesser effect on insulin action in the liver.

Thiazolidinediones act by binding to and activating a specific transcription factor in the nucleus of the cell.^{50,51} When activated, this factor binds to specific genes and either stimulates or inhibits their transcription. Some of these genes regulate proteins involved in adipose tissue differentiation, lipid metabolism, and the intracellular insulin action cascade.

Thiazolidinediones improve insulin action in patients with type 2 diabetes by approximately 25% to 40%, depending on the population studied.^{52,53} They also decrease

Metformin lowers fasting hyperglycemia, but not postprandial

circulating free fatty acid levels approximately 25%,⁵² and this is one of the mechanisms thought responsible for the decrease in insulin resistance.

A major effect of thiazolidinediones is the differentiation of stem cells into adipocytes. This occurs in subcutaneous adipose tissue, but not in visceral adipose tissue,⁵⁴ and accounts for some of the weight gain associated with thiazolidinedione therapy.

The mean decrease in hemoglobin A_{1c} with thiazolidinedione therapy is 1.5 percentage points. These drugs also mitigate many of the features of the metabolic (insulin resistance) syndrome (TABLE 4),^{12,49} such as diabetic dyslipidemia and the procoagulant state. Therefore, it is reasonable to speculate that these drugs will reduce the incidence of cardiovascular diseases. A number of in vitro and small in vivo animal and human studies support such a conclusion. Several large clinical outcome studies are under way to test this hypothesis definitively.

Moreover, thiazolidinediones might preserve beta cell function. The UKPDS⁹ demonstrated that neither sulfonylureas, metformin, nor dietary treatments had any effect on the progressive deterioration of pancreatic beta cell function. Studies in animal models of insulin-resistant diabetes⁵⁵ and preliminary studies in humans raise the possibility that long-term treatment with thiazolidinediones may slow such deterioration. Several long-term clinical trials are under way to examine this.

Adverse effects of thiazolidinediones.

The major adverse effects of the thiazolidinediones are fluid retention and weight gain.^{48,49}

As monotherapy, both rosiglitazone and pioglitazone cause a modest increase in plasma volume and are reported to cause mild to moderate edema in 4% to 5% of patients. When a thiazolidinedione is taken with a sulfonylurea, 6% to 7% of patients develop edema; when it is taken with insulin, approximately 15% of patients develop edema.

Occasionally, congestive heart failure develops during thiazolidinedione treatment, but there are no published data to define either the prevalence or the relationship of this to drug therapy. It is not unreasonable to suspect that an increase in plasma volume

might precipitate clinical congestive heart failure in patients who have cardiovascular disease and are in borderline compensation. Thiazolidinediones are not recommended in patients with New York Heart Association functional class III or IV heart failure.

Weight gain is due to an increase in subcutaneous adipose tissue and in fluid retention. Monotherapy is associated with a weight gain of 1.6 to 3.5 kg in the first year. A slightly greater weight gain occurs when a thiazolidinedione is combined with a sulfonylurea or insulin. Rarely and for unknown reasons, some patients develop severe edema, gain 10 to 20 kg, or both.

Hepatotoxicity was seen with troglitazone, an earlier thiazolidinedione, and was responsible for its removal from the market, but it does not appear to occur with rosiglitazone or pioglitazone.⁵⁶ However, as a precaution, patients receiving thiazolidinediones should undergo baseline and periodic monitoring of liver enzymes. These drugs should not be given to patients with baseline alanine aminotransferase (ALT) levels 2.5 or more times the upper limit of the normal range. Persistence of ALT levels more than three times the upper limit of the normal range during therapy is an indication to stop the drug.

Role of insulin sensitizers in type 2 diabetes

Insulin sensitizers improve hyperglycemia by decreasing insulin resistance. Their unique contribution to the management of type 2 diabetic patients is that they treat many of the components of the metabolic syndrome (dyslipidemia, procoagulant state, endothelial dysfunction, inflammatory responses) and reduce the risk for cardiovascular complications. For metformin, this has been shown to result in fewer clinical cardiovascular events.

■ ALPHA-GLUCOSIDASE INHIBITORS

The alpha-glucosidase inhibitors acarbose (Precose) and miglitol (Glyset) competitively inhibit digestion of oligosaccharides to monosaccharides, so that glucose is slowly absorbed throughout the length of the small intestine, rather than rapidly in the proximal jejunum.^{57,58} Advantages:

- They specifically lower postprandial plas-

**UKPDS: Fewer
MIs, deaths
with metformin
vs lifestyle
modification**



- ma glucose levels
- Their action is independent of and additive to all other forms of pharmacologic therapy
- They do not cause weight loss or gain
- They are relatively nontoxic.^{57,58}

When given to patients already taking insulin, sulfonylureas, or metformin, the alpha-glucosidase inhibitors decrease maximal postprandial plasma glucose levels by approximately 50 mg/dL and hemoglobin A_{1c} by approximately 0.5 percentage points.^{59,60}

Alpha-glucosidase inhibitors must be given with the start of each meal. They are effective only if more than 40% of the calories in the diet come from complex carbohydrates—a high content.⁵⁷

If hypoglycemia occurs when an alpha-glucosidase inhibitor is used in combination with insulin or a sulfonylurea, glucose—not disaccharides—must be given because of the delayed digestion of complex carbohydrates.

Side effects. The major disadvantage of alpha-glucosidase inhibitors is their gastrointestinal side effects, which include abdominal discomfort, flatulence, and, occasionally, diarrhea.^{59,60} These effects are due to carbohydrate spilling into the colon, where it is fermented by bacteria. These side effects can be minimized by starting with very small doses with the evening meal and titrating upward very slowly. This allows the distal jejunum and ileum time to increase their normally low concentrations of alpha-glucosidase enzymes, so that the oligosaccharides that reach those segments can be digested.

■ CHANGING GOALS OF THERAPY

The goals of therapy for patients with type 2 diabetes have changed in the last several years.

Trials show that chronic vascular complications increase in prevalence and severity with the duration of type 1 and type 2 diabetes and with the magnitude of hyperglycemia, beginning at hemoglobin A_{1c} levels above the mean normal value (ie, > 5.2%).^{61,62} This means that the ideal goal for glycemic control should be a hemoglobin A_{1c} level as close to 6.0% as possible without causing serious side effects. The American Diabetes Association

sets the goal as less than 7.0%; the European Diabetes Association and the American Association of Clinical Endocrinologists set the goal at 6.5% or lower.

Plasma glucose levels that correspond to a hemoglobin A_{1c} level of 6.5% are a fasting level less than 110 mg/dL and a 2-hour postprandial level less than 140 mg/dL.

The exact goal should be tailored to the individual patient, based on his or her clinical characteristics.

Blood pressure and lipid control

The goal for blood pressure control in diabetic patients is 130/80 mm Hg or lower.⁶³

The goals for the management of dyslipidemia as defined by the ATP III of the National Cholesterol Education Program¹⁵ are a low-density lipoprotein cholesterol level lower than 100 mg/dL, with no specific goals for plasma triglycerides or high-density lipoprotein cholesterol. However, studies suggest that a target plasma triglyceride level of 150 mg/dL or lower and a plasma high-density lipoprotein cholesterol level of 40 mg/dL or higher are desirable.

■ EFFECTS ON GLYCEMIC CONTROL

The effect of all antihyperglycemic agents on overall glycemic control as measured by reduction in hemoglobin A_{1c} depends on the baseline hemoglobin A_{1c} level.⁴⁹ Interventional studies with rosiglitazone, metformin, and insulin secretagogues have shown that they decrease mean hemoglobin A_{1c} by 1.5 to 2.0 percentage points vs placebo when the baseline hemoglobin A_{1c} is between 8.5% and 9.5%, but only about 1 percentage point when the baseline is between 6.5% and 7.5%.⁴⁸

Chronic plasma glucose levels over 300 mg/dL have direct inhibitory effects on insulin secretion and cause some impairment of insulin action.⁶⁴ Any treatment of hyperglycemia decreases glucose toxicity as it lowers hyperglycemia.

Agents that have major effects in decreasing fasting plasma glucose levels (sulfonylureas, repaglinide, metformin, pioglitazone, rosiglitazone) lowered mean hemoglobin A_{1c} levels 1.5 to 2.0 percentage points vs placebo in the registration studies submitted

Diabetes goals:

- A_{1c} ≤ 6.5 or 7
- BP ≤ 130/80
- LDL < 100

to the US Food and Drug Administration (FDA).⁴⁸

In the few comparative studies available (metformin vs glyburide, repaglinide vs glyburide, rosiglitazone vs glyburide), these agents appeared to be equally effective in decreasing hemoglobin A_{1c}, though they have different mechanisms.^{45,65} There are no direct comparative studies demonstrating the superiority of any single agent in decreasing hemoglobin A_{1c}.

Agents that primarily lower postprandial hyperglycemia (alpha-glucosidase inhibitors, nateglinide) decreased mean hemoglobin A_{1c} 0.5 to 1.0 percentage points compared with placebo in registration studies presented to the FDA.⁴⁸

Insulin supplementation can lower hemoglobin A_{1c} to any desired level, but its use is limited by unacceptable rates of severe hypoglycemia.

Monotherapy or combination therapy?

The degree to which a single drug can achieve glycemic control is limited by its intrinsic antihyperglycemic activity, by the patient's residual beta cell function, and by its side effects. Consequently, monotherapy achieves target glycemic control in type 2 diabetic patients with only mild elevations of hemoglobin A_{1c} (probably no higher than 7.0%).

The agent of choice for these patients should be one that does not cause hypoglycemia, ie, metformin, a thiazolidinedione, or an alpha-glucosidase inhibitor. The concomitant presence of the metabolic syndrome would dictate the use of an insulin sensitizer. If an insulin secretagogue were to be used, a rapid, short-acting one would be preferable to minimize late hypoglycemia. Recent studies⁶⁶ found that monotherapy with metformin decreased the rate of progression from impaired glucose tolerance to type 2 diabetes over 3 years by 31%, and acarbose decreased it by 25%.

More severe elevations of hemoglobin A_{1c} are best treated with combinations of submaximal doses of two or more agents, each of which corrects hyperglycemia by a different mechanism. Type 2 diabetic patients with severe insulin deficiency require either bedtime insulin as a component of their treatment or intensive insulin replacement therapy.

COMBINATION THERAPY OF TYPE 2 DIABETES

The most effective treatment of moderate hyperglycemia (hemoglobin A_{1c} 7% to 8%) or severe hyperglycemia (hemoglobin A_{1c} > 8%) is a combination either of oral agents that have different modes of action or of oral agents with insulin replacement.⁴⁸

Combinations of oral agents

Combination oral therapy usually involves an insulin sensitizer and an insulin secretagogue. The addition of the second agent usually lowers the mean hemoglobin A_{1c} level 1.0 to 1.4 percentage points more than monotherapy when the baseline value is between 8.5% and 9.5%.⁴⁸ Data are available on glyburide-metformin, repaglinide-metformin, nateglinide-metformin, sulfonylurea-pioglitazone, sulfonylurea-rosiglitazone, repaglinide-pioglitazone, and repaglinide-rosiglitazone.^{48,67-70} From 30% to 50% of patients taking these regimens lower their hemoglobin A_{1c} levels to 7.0% or less.

Some combinations can be given in a single pill: eg, glyburide and metformin (Glucovance). The advantage of a single pill is lower cost, a single copayment for the patient, and better compliance. The disadvantage is the fixed ratio of the drugs, which rules out dosage adjustment of an individual agent.

Combination therapy can start with submaximal doses of each agent, or after the dose of the first agent has been maximized. Few data are available to prove which approach is better, but starting with a combination has the potential advantages of more expeditious control of glycemia and fewer side effects.

Metformin plus a thiazolidinedione has been shown to improve glycemic control, lowering hemoglobin A_{1c} by 1.0 to 1.2 percentage points compared with maximum doses of either drug alone, when the mean baseline hemoglobin A_{1c} level was between 8.5% and 9.5%.^{67,70} This additive benefit in glycemic control occurs because these agents improve insulin resistance by different mechanisms and in different tissues.

Combination regimens lower A_{1c} levels to 7.0% or less in 30%–50% of patients



Adding a third or fourth oral agent

One can consider adding a third or fourth oral drug with yet another mechanism of action if the hemoglobin A_{1c} level achieved with two agents is 8.0% or less, since one may anticipate a potential decrease of approximately 0.5 to 1.3 percentage points, which could bring the value to below 7.0%.

However, if the hemoglobin A_{1c} on two agents is above 8.0%, the likelihood that adding a third oral agent will bring it to the target range is small, and adding bedtime insulin replacement is more likely to result in target glycemic control.

The third agent could be an alpha-glucosidase inhibitor; if the patient has been tak-

ing an insulin secretagogue and an insulin sensitizer, the third agent could be another insulin sensitizer.

Combining oral therapy with insulin replacement

The addition of an insulin sensitizer to full insulin replacement therapy lowers the hemoglobin A_{1c} level by approximately 1.3 percentage points while reducing the required insulin dose by 20% to 25%.

The cost of combination therapy must be considered in addition to the potential benefits. The combination of three oral antihyperglycemic agents is likely to cost more than bedtime insulin replacement and a daytime insulin sensitizer.



REFERENCES

- Amos AF, McCarty DJ, Zimmet P. The rising global burden of diabetes and its complications: estimates and projections to the year 2010. *Diabet Med* 1997; 14(suppl):7–85.
- Aiello LP, Cavallerano JD, Gardner TW, et al. Diabetic retinopathy. *Diabetes Care* 1998; 21:143–156.
- Centers for Disease Control and Prevention. 1999 Diabetes Surveillance Report. Chapter 8: End Stage Renal Disease. Available at www.cdc.gov/diabetes/statistics/surv199/chap8/contents.htm. Accessed 5/8/02.
- Mayfield JA, Janisse D, Reiber GE, Pogach LM, Sanders LJ. Preventive foot care in people with diabetes. *Diabetes Care* 1998; 21:2161–2177.
- Wingard DL, Barrett-Connor E. Heart disease and diabetes. In: *Diabetes in America*. 2nd ed. NIH Publication No. 95-1468. 1995:429–448.
- Bergstrom RW, Wahl PW, Leonetti DI, Fujimoto WY. Association of fasting glucose levels with a delayed secretion of insulin after oral glucose in subjects with glucose intolerance. *J Clin Endocrinol Metab* 1990; 71:1447–1453.
- Lebovitz HE. Insulin secretagogues: old and new. *Diabetes Reviews* 1999; 7:139–153.
- Kahn SE, Prigeon RL, McCulloch DK, et al. Quantification of the relationship between insulin sensitivity and beta-cell function in human subjects. Evidence for a hyperbolic function. *Diabetes* 1993; 42:1663–1672.
- UK Prospective Diabetes Study Group. Overview of 6 years therapy of type 2 diabetes: a progressive disease (UKPDS 16). *Diabetes* 1995; 44:1249–1258.
- Haffner SM, Stern MP, Hazuda HP, Mitchell BD, Patterson JK. Cardiovascular risk factors in confirmed prediabetic individuals: does the clock for coronary heart disease start ticking before the onset of clinical diabetes? *JAMA* 1990; 263:2893–2898.
- Weyer C, Bogardus C, Mott DM, Pratley RE. The natural history of insulin secretory dysfunction and insulin resistance in the pathogenesis of type 2 diabetes mellitus. *J Clin Invest* 1999; 104:787–794.
- Lebovitz HE. Insulin resistance: definition and consequences. *Exp Clin Endocrinol Diabetes* 2001; 109(suppl 2):135–148.
- Isomaa B, Almgren P, Tuomi T, et al. Cardiovascular morbidity and mortality associated with the metabolic syndrome. *Diabetes Care* 2001; 24:683–689.
- Haffner SM, Mykkanen L, Festa A, Burke JP, Stern MP. Insulin-resistant prediabetic subjects have more atherogenic risk factors than insulin-sensitive prediabetic subjects. Implications for preventing coronary heart disease during the prediabetic state. *Circulation* 2000; 101:975–980.
- Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults. Executive summary of the third report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). *JAMA* 2001; 285:2486–2497.
- van Haeften TW, Pimenta W, Mitrakou A, et al. Relative contributions of beta-cell function and tissue insulin sensitivity to fasting and postglucose-load glycemia. *Metabolism* 2000; 49:1318–1325.
- Dostou J, Gerich J. Pathogenesis of type 2 diabetes mellitus. *Exp Clin Endocrinol Diabetes* 2001; 109(suppl 2):149–156.
- Aguiar-Bryan L, Bryan J, Nakazaki M. Of mice and men: K_{ATP} channels and insulin secretion. *Recent Prog Horm Res* 2001; 56:47–68.
- Clark HE, Matthews DR. The effect of glimepiride on pancreatic beta-cell function under hyperglycaemic clamp and hyperinsulinaemic, euglycaemic clamp conditions in non-insulin-dependent diabetes mellitus. *Horm Metab Res* 1996; 28:445–450.
- Ashcroft FM. Mechanisms of the glycaemic effects of sulfonylureas. *Horm Metab Res* 1996; 28:456–463.
- Shapiro ET, Van Cauter E, Tillil H, et al. Glyburide enhances the responsiveness of the beta cell to glucose but does not correct the abnormal patterns of insulin secretion in non-insulin-dependent diabetes mellitus. *J Clin Endocrinol Metab* 1989; 69:571–576.
- Fuhrendorff J, Rorsman P, Kofod H, et al. Stimulation of insulin release by repaglinide and glibenclamide involves both common and distinct processes. *Diabetes* 1998; 47:345–351.
- Hu S, Wang S, Dunning BE. Tissue selectivity of antidiabetic agent nateglinide: study on cardiovascular and beta-cell K_{ATP} channels. *J Pharmacol Exp Ther* 1999; 291:1372–1379.
- Hu S, Wang S, Fanelli B, et al. Pancreatic beta-cell K_{ATP} channel activity and membrane-binding studies with nateglinide: a comparison with sulfonylureas and repaglinide. *J Pharmacol Exp Ther* 2000; 293:444–452.
- Hatorp V, Huang WC, Strange P. Pharmacokinetic properties of repaglinide in elderly subjects with type 2 diabetes. *J Clin Endocrinol Metab* 1999; 84:1475–1478.
- Walter YH, Spratt DI, Garreffa S, McLeod JF. Mealtime glucose regulation by nateglinide in type-2 diabetes mellitus. *Eur J Clin Pharmacol* 2000; 56:129–133.
- Hanefeld M, Dickinson S, Bouter KP, Guitard C. Rapid and short-acting mealtime insulin secretion with nateglinide controls both



- prandial and mean glycemia. *Diabetes Care* 2000; 23:202–207.
28. **Guay DRP.** Repaglinide, a novel, short-acting hypoglycemic agent for type 2 diabetes mellitus. *Pharmacotherapy* 1998; 18:1195–1204.
 29. **Damsbo P, Marbury TC, Clauson P, Windfeld K.** A double-blind randomized comparison of meal-related glycemic control by repaglinide and glyburide in well-controlled type 2 diabetic patients. *Diabetes Care* 1999; 22:789–794.
 30. **Jovanovic L, Dailey G III, Huang W-C, Strange P, Goldstein BJ.** Repaglinide in type 2 diabetes: A 24-week fixed-dose efficacy and safety study. *J Clin Pharmacol* 2000; 40:49–57.
 31. **UK Prospective Diabetes Study Group.** Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). *Lancet* 1998; 352:837–853.
 32. **Abraira C, Henderson WG, Colwell JA, et al.** Response to intensive therapy steps and to glipizide dose in combination with insulin in type 2 diabetes. VA feasibility study on glycemic control and complications (VA CSDM). *Diabetes Care* 1998; 21:574–579.
 33. **Yki-Jarvinen H, Ryysy L, Nikkila K, Tulokas T, Vanamo R, Heikkila M.** Comparison of bedtime insulin regimens in patients with type 2 diabetes mellitus: a randomized, controlled trial. *Ann Intern Med* 1999; 130:389–396.
 34. **Mudaliar S, Edelman SV.** Insulin therapy in type 2 diabetes. *Endocrinol Metab Clin North Am* 2001; 30:935–982.
 35. **Yki-Jarvinen H, Dressler A, Ziemann M, Study Group HOE 901/3002.** Less nocturnal hypoglycemia and better post-dinner glucose control with bedtime insulin glargine compared with bedtime NPH insulin during combination therapy in type 2 diabetes. *Diabetes Care* 2001; 23:1130–1136.
 36. **Bolli G.** Physiological insulin replacement in type 1 diabetes mellitus. *Exp Clin Endocrinol Diabetes* 2001; 109(suppl 2):317–332.
 37. **Bolli G, Owens DR.** Insulin glargine. *Lancet* 2000; 356:443–445.
 38. **Skyler JS.** Insulin treatment. In: Lebovitz H, editor. *Therapy for Diabetes Mellitus and Related Disorders*. 3rd ed. Alexandria, Va: American Diabetes Association, 1998:186–203.
 39. **Stumvoll M, Nurjhan N, Perriello G, Dailey G, Gerich J.** Metabolic effects of metformin in non-insulin-dependent diabetes mellitus. *N Engl J Med* 1995; 333:550–554.
 40. **Hundal RS, Krssak M, Dufour S, et al.** Mechanism by which metformin reduces glucose production in type 2 diabetes. *Diabetes* 2000; 49:2063–2069.
 41. **Bell PM, Hadden DR.** Metformin. *Endocrinol Metab Clin North Am* 1997; 26:523–537.
 42. **Campbell IW, Howlett HCS.** Worldwide experience of metformin as an effective glucose-lowering agent: a meta-analysis. *Diabetes Metab Rev* 1995; 11(suppl):57–62.
 43. **Inzucchi SE, Maggs DG, Spollett GR, et al.** Efficacy and metabolic effects of metformin and troglitazone in type 2 diabetes mellitus. *N Engl J Med* 1998; 338:867–872.
 44. **Yu JG, Kruszynska YT, Mulford MI, Olefsky JM.** A comparison of troglitazone and metformin on insulin requirements in euglycemic intensively insulin-treated type 2 diabetic patients. *Diabetes* 1999; 48:2414–2421.
 45. **DeFronzo RA, Goodman AM.** Efficacy of metformin in patients with non-insulin-dependent diabetes mellitus. *N Engl J Med* 1995; 333:541–549.
 46. **Bailey CJ, Turner RC.** Drug therapy: metformin. *N Engl J Med* 1996; 334:574–579.
 47. **UK Prospective Diabetes Study Group.** Effect of intensive blood glucose control with metformin on complications in overweight patients with type 2 diabetes (UKPDS 34). *Lancet* 1998; 352:854–865.
 48. **Lebovitz HE.** Oral therapies for diabetic hyperglycemia. *Endocrinol Metab Clin North Am* 2001; 30:909–933.
 49. **Lebovitz HE, Banerji MA.** Insulin resistance and its treatment by thiazolidinediones. *Recent Prog Horm Res* 2001; 56:265–294.
 50. **Willson TM, Brown PJ, Sternbach DD, Henke BR.** The PPARs: from orphan receptors to drug discovery. *J Med Chem* 2000; 43:527–550.
 51. **Willson TM, Lambert MH, Kliewer SA.** Peroxisome proliferator-activated receptor gamma and metabolic disease. *Annu Rev Biochem* 2001; 70:341–367.
 52. **Lebovitz HE, Dole JF, Patwardhan R, Rappaport EB, Freed MI.** Rosiglitazone monotherapy is effective in patients with type 2 diabetes. *J Clin Endocrinol Metab* 2001; 86:280–288.
 53. **Miyazaki Y, Ferrannini E, Mahankali A, et al.** Improved glycemic control and enhanced insulin sensitivity in type 2 diabetic subjects treated with pioglitazone. *Diabetes Care* 2001; 24:710–719.
 54. **Adams M, Montague CT, Prins JB, et al.** Activators of PPAR-gamma have depot-specific effects on human pre-adipocyte differentiation. *J Clin Invest* 1997; 100:3149–3153.
 55. **Finegood DT, McArthur MD, Kojwang D, et al.** Beta-cell mass dynamics in Zucker diabetic fatty rats; rosiglitazone prevents the rise in net cell death. *Diabetes* 2001; 50:1021–1029.
 56. **Lebovitz HE, Kreider M, Freed MI.** Evaluation of liver function in type 2 diabetic patients during clinical trials: evidence that rosiglitazone does not cause hepatic dysfunction. *Diabetes Care* 2002; 25:815–823.
 57. **Lebovitz HE.** Alpha-glucosidase inhibitors as agents in the treatment of diabetes. *Diabetes Reviews* 1998; 6:132–145.
 58. **Raptis SA, Dimitriadis GD.** Oral hypoglycemic agents: insulin secretagogues, alpha-glucosidase inhibitors and insulin sensitizers. *Exp Clin Endocrinol Diabetes* 2001; 109(suppl 2):265–287.
 59. **Chiasson JL, Josse R, Hunt J, et al.** The efficacy of acarbose in the treatment of patients with non-insulin-dependent diabetes mellitus. *Ann Intern Med* 1994; 121:928–935.
 60. **Holman RR, Cull CA, Turner RC.** A randomized double-blind trial of acarbose in type 2 diabetes shows improved glycemic control over 3 years. *Diabetes Care* 1999; 22:960–964.
 61. **DCCT Research Group.** The absence of a glycemic threshold for the development of long-term complications: the perspective of the diabetes control and complications trial. *Diabetes* 1996; 45:1289–1298.
 62. **Stratton IM, Adler AI, Neil HA, et al.** Association of glycemia with macrovascular and microvascular complications of type 2 diabetes (UKPDS 35): prospective observational study. *BMJ* 2000; 321:405–412.
 63. **American Diabetes Association.** Standards of medical care for patients with diabetes mellitus. *Diabetes Care* 2002; 25(suppl A):S33–S49.
 64. **Boden G, Ruiz J, Kim CJ, Chen Y.** Effects of prolonged glucose infusion on insulin secretion, clearance and action in normal subjects. *Am J Physiol* 1996; 270:E251–E258.
 65. **Marbury T, Huang W-C, Strange P, Lebovitz HE.** Repaglinide vs glyburide: a 1-year comparison trial. *Diabetes Res Clin Pract* 1999; 43:155–166.
 66. **Diabetes Prevention Program Research Group.** Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. *N Engl J Med* 2002; 346:393–403.
 67. **Fonseca V, Rosenstock J, Patwardhan R, Salzman A.** Effect of metformin and rosiglitazone combination therapy in patients with type 2 diabetes mellitus. A randomized controlled trial. *JAMA* 2000; 283:1695–1702.
 68. **Horton ES, Foley J, Clinkingbeard C, Foley J, Mallow S, Shen S.** Nateglinide alone and in combination with metformin improves glycemic control by reducing mealtime glucose levels in type 2 diabetes. *Diabetes Care* 2000; 23:1660–1665.
 69. **Horton ES, Whitehouse F, Ghazzi MN, Venable TC, The Troglitazone Study Group, Whitcomb RW.** Troglitazone in combination with sulfonylurea restores glycemic control in patients with type 2 diabetes. *Diabetes Care* 1998; 21:1462–1469.
 70. **Einhorn D, Rendell M, Rosenzweig J, Egan JW, Mathisen AL, Schneider RL.** Pioglitazone hydrochloride in combination with metformin in the treatment of type 2 diabetes mellitus: a randomized, placebo-controlled study. *Clin Ther* 2000; 22:1395–1409.

ADDRESS: Harold E. Lebovitz, MD, 416 Henderson Avenue, Staten Island, NY 10310.