Oral Antihyperglycemic Therapy for Type 2 Diabetes

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SCIENTIFIC REVIEW
AND CLINICAL APPLICATIONS

EPIDEMIOLOGY

Diabetes mellitus affects more than 6% of the US population, with the great majority having type 2 diabetes mellitus (DM).1 In some older groups, the prevalence of DM and its metabolic forerunner, impaired glucose tolerance (IGT), approaches 25%.2 Throughout the past decade, a 30% increase in the prevalence of DM has been recorded in the United States, with the most dramatic increase in younger individuals.3 When the long-term complications of this disease and their costs are considered, the implications of these statistics are sobering.4

The importance of blood glucose control in preventing microvascular complications of DM, such as retinopathy and nephropathy, is now recognized.5,6 Whether such a relationship exists for macrovascular complications, such as myocardial infarction and stroke, is less clear.7 Simultaneously, a rapidly expanding therapeutic armamentarium is now available to treat hyperglycemia in type 2 DM. The number of oral antihyperglycemic agent classes, each with its unique mechanism of action, has increased 5-fold throughout the past 6 years—an often confusing increase in new categories of drugs: biguanides, α-glucosidase inhibitors, thiazolidinediones (TZDs), and nonsulfonylurea insulin secretagogues.

See also pp 373 and 379.

Context Care of patients with type 2 diabetes has been revolutionized throughout the past several years—first, by the realization of the importance of tight glycemic control in forestalling complications, and second, by the availability of several unique classes of oral antidiabetic agents. Deciphering which agent to use in certain clinical situations is a new dilemma facing the primary care physician.

Objective To systematically review available data from the literature regarding the efficacy of oral antidiabetic agents, both as monotherapy and in combination.

Data Sources A MEDLINE search was performed to identify all English-language reports of unique, randomized controlled clinical trials involving recently available oral agents for type 2 diabetes. Bibliographies were also reviewed to find additional reports not otherwise identified.

Study Selection and Data Extraction Studies (63) were included in the analysis if they had a study period of at least 3 months; if each group contained at least 10 subjects at the study’s conclusion; and if hemoglobin A1c was reported. When multiple dosages of a drug were tested, the results of the highest approved dosage were used. In placebo-controlled trials, hemoglobin A1c data are presented as the difference between the change in treated vs placebo subjects.

Data Synthesis Five distinct oral drug classes are now available for the treatment of type 2 diabetes. Compared with placebo treatment, most of these agents lower hemoglobin A1c levels approximately 1% to 2%. Equivalent efficacy is usually demonstrated when different agents are compared with one another in the same study population. When they are used in combination, there are additional glycemic benefits. Long-term vascular risk reduction has been demonstrated only with sulfonylureas and metformin.

Conclusions With few exceptions, the available oral antidiabetic agents are equally effective at lowering glucose concentrations. Their mechanisms of action are different, however, and as a result they appear to have distinct metabolic effects. These are reflected in their adverse effect profiles and their effect on cardiovascular risk, which may influence drug choice.

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More therapeutic options translate into more complex decision making for primary care physicians and diabetic patients. In this article I review the individual oral-agent drug classes and the published evidence demonstrating their effectiveness.
efficacy in lowering glucose concentrations as well as their effectiveness in preventing diabetic complications.

METHODS
A MEDLINE search was performed to identify all English-language articles of unique, randomized controlled clinical trials involving recently available oral agents for type 2 DM. Bibliographies were also reviewed to find additional reports not otherwise identified. Studies (63) were included in the analysis if they met the following criteria: study period of at least 3 months, each group containing at least 10 subjects at the study’s conclusion, and hemoglobin A1c (HbA1c) reported. When multiple doses of a drug were tested, the results of the highest approved dose were used. In placebo-controlled trials, HbA1c data are presented by convention as the difference between the change in treated vs placebo subjects.

PATHOGENESIS OF TYPE 2 DM
Knowledge of the pathogenesis of type 2 DM is important in understanding the appropriate role for each oral-agent class. Type 2 DM is a complex metabolic disorder resulting from relatively decreased pancreatic insulin secretion and variable contributions of decreased insulin action, or insulin resistance, in target tissues, mainly muscle and the liver. Insulin resistance is first demonstrated in skeletal muscle, in which higher concentrations of insulin are necessary to allow glucose to enter cells. Peripheral insulin resistance predicts the development of type 2 DM and is detected in normoglycemic first-degree relatives of patients with type 2 DM. It is influenced by both genetic and environmental (eg, obesity) factors. Insulin-resistant individuals frequently exhibit a constellation of other characteristics, including visceral obesity, dyslipidemia, hypertension, hyperinsulinemia, impaired fibrinolysis, endothelial dysfunction, hyperuricemia, vascular inflammation, and premature atherosclerosis. They are said to have the metabolic syndrome, or insulin resistance syndrome, emphasizing the presumed central pathogenic role of insulin resistance.

Initially, in the face of insulin resistance, compensatory increases in pancreatic insulin secretion are able to maintain normal glucose concentrations. However, as the disease progresses, insulin production gradually diminishes, leading to progressive stages of hyperglycemia. Hyperglycemia is first exhibited in the postprandial state, since uptake by skeletal muscle is the metabolic fate of the majority of ingested carbohydrate energy, and then during fasting. As insulin secretion decreases, hepatic glucose production, normally attenuated by insulin, increases. This increase is primarily responsible for the elevation of fasting glucose levels in patients with type 2 DM. Superimposed upon these mechanisms is the well-recognized deleterious effect of hyperglycemia itself—glucotoxicity—upon both insulin sensitivity and insulin secretion.

Adipose tissue plays an important but often overlooked role in the pathogenesis of type 2 DM. Insulin resistance is also demonstrated at the adipocyte level, leading to unrestrained lipolysis and elevation of circulating free fatty acids. Increased free fatty acids, in turn, further dampen the insulin response in skeletal muscle, while further impairing pancreatic insulin secretion as well as augmenting hepatic glucose production (“lipotoxicity”). Therefore, type 2 DM results from coexisting defects at multiple organ sites: resistance to insulin action in muscle, defective pancreatic insulin secretion, and unrestrained hepatic glucose production, all of which are worsened by defective insulin action in fat (FIGURE). These pathophysiological lesions are to blame for the development and progression of hyperglycemia. They are also the primary targets for pharmacological therapy.

THE IMPORTANCE OF GLYCEMIC CONTROL
The American Diabetes Association’s recommended targets for glycemic control include a preprandial blood glucose level of 80 to 120 mg/dL (4.4 to 6.7 mmol/L), a bedtime blood glucose level of 100 to 140 mg/dL (5.6 to 7.8 mmol/L), and an HbA1c level of less than 7%. More stringent guidelines have recently been offered by the American College of Endocrinology and the American Association of Clinical Endocrinologists: preprandial blood glucose levels less than 110 mg/dL (6.1 mmol/L), 2-hour postprandial glucose levels less than 140 mg/dL (7.8 mmol/L), and HbA1c levels at 6.5%. These recommendations are based on findings from 3 landmark studies: the Diabetes Control and Complications Trial,7 the Kumamoto Study,8 and the United Kingdom Prospective Diabetes Study (UKPDS),9 which have shown unequivocally that maintaining blood glucose concentrations as close to normal as possible in both type 1 and type 2 DM decreases the incidence of microvascular complications.

Nonpharmacological Therapy
Diet, exercise, and weight loss are at the center of any therapeutic program. Not only do these lifestyle modifications lower blood glucose concentrations, but they also ameliorate many of the frequently coexisting risk factors for cardiovascular disease. Unfortunately, most patients are unable to achieve adequate control with lifestyle interventions alone, which should not detract from their critical role, since they enhance the effectiveness of medical regimens. A controlled-energy diet and regular aerobic exercise are therefore recommended for the majority of patients with type 2 DM, who are usually overweight.22,23

Pharmacological Therapy
Sulfonylureas. Sulfonylurea (SU) drugs have been available in the United States since 1954. Second-generation SUs (gliburide, glipizide, and glimepiride) are more potent and probably safer than first-generation SUs (chlorpropamide, tolbutamide, aceclohexamide, and tolazamide) but essentially of equal efficacy. The SUs bind to the SU re-
ceptor, found on the surface of pancreatic beta cells. This interaction leads to a closure of voltage-dependent potassium adenosinetriphosphate (K<sub>ATP</sub>) channels, facilitating cell membrane depolarization, calcium entry into the cell, and insulin secretion. Thus, SUs allow for insulin release at lower glucose thresholds than normal. They partially reverse the attenuated insulin secretion that characterizes type 2 DM. Understandably, in the face of SU therapy, circulating insulin concentrations are increased. As a result, and despite the presence of insulin resistance, glucose concentrations fall. The possibility that such agents may also directly enhance peripheral glucose disposal (ie, decrease insulin resistance) has also been raised. However, the peripheral effects of SUs are most likely secondary to a reduction in glucotoxicity.

When compared with placebo, SU therapy leads to a mean decrease in HbA<sub>1c</sub> of approximately 1% to 2% (TABLE 1). One study demonstrated a more impressive change, but the rise in HbA<sub>1c</sub> level experienced by the placebo group was greater than usual, reaching 2%. Current agents are equally efficacious and vary subtly, such as in their metabolism and duration of action. The newest member of this class, glimepiride, binds less avidly in cardiac tissues, which contain K<sub>ATP</sub> channels similar to those of beta cells. Glimepiride, therefore, may reduce ischemic preconditioning less than the other SUs do, the clinical importance of which is unclear. In general, there is no consistent additional benefit on coexisting conditions, such as elevated lipid levels or blood pressure. Given the epidemiological association between hyperinsulinemia and cardiovascular disease, some have raised concerns that SUs increase cardiovascular morbidity. The mechanism of action and frequent loss of efficacy over time, another concern is their potential to exhaust beta cell function. However, as demonstrated in the UKPDS, the inexorable decline in beta cell function may be an underlying characteristic of the diabetic state itself, independent of treatment modality. Of more practical concern, SU therapy is associated with 2 common adverse effects. The first is weight gain, typically from 2 to 5 kg, problematic in...
a group of patients frequently already overweight. The second is hypoglycemia, most likely to affect the elderly, those with worsening renal function, and those with irregular meal schedules.

In the UKPDS, 4209 patients newly diagnosed with type 2 DM were randomized to either intensive (medication) or conventional (diet) treatment and observed for approximately 10 years. The intensive-treatment group underwent a subsequent randomization to primary therapy with SU or insulin. When compared with conventional therapy, intensive treatment was associated with a decreased risk of predominantly microvascular complications, including a 12% reduction in any diabetes-related end point ($P = .03$) and a 25% reduction in all microvascular end points ($P < .001$). There was no significant effect on diabetes-related death or on all-cause mortality, however, and there was only a trend toward a small effect (−16%) on the risk of myocardial infarction ($P = .05$). Overall, there were no significant differences between SU-treated subjects and those treated with insulin. One might argue that improved glycemic control from SUs did not significantly decrease macrovascular risk because this effect was negated by the opposing effect of hypoinsulinemia.

Optimal dosing of each member of this class varies. As a general rule, however, glucose-lowering effect plateaus after half the maximal recommended

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<td>Hanefeld et al,’ 2000</td>
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<td>Goldberg et al,’ 1998</td>
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*UKPDS indicates United Kingdom Prospective Diabetes Study; GITS, gastrointestinal transport system; and SU, sulfonylurea.
†Values represent the placebo-adjusted absolute percentage reduction in the active therapy group, adjusted for placebo. Because of different recruitment criteria for individual studies, particularly regarding baseline hemoglobin $A_1C$, direct comparison of one agent with another is difficult.
dose is reached. Most agents undergo metabolism by the liver and are cleared by the kidney. Therefore, they must be used cautiously in those with advanced forms of either hepatic or renal impairment. Sulfonylureas are approved for use as monotherapy and in combination with all other oral agent classes (except the non-SU secretagogues) and insulin.

**Biguanides.** Although available internationally for decades, metformin, a biguanide, was not released in the United States until 1995. An earlier biguanide, phenformin, was removed from the market in the 1970s because of an association with lactic acidosis. In contrast to the SUs, metformin does not stimulate insulin secretion. The precise mode of action of metformin remains somewhat controversial, but its predominant effect is to reduce hepatic glucose production in the presence of insulin. It is therefore considered an insulin sensitizer. Increased peripheral glucose disposal has also been measured, although this is most likely a secondary phenomenon caused by lowering of gluco toxicity and not a direct effect of the drug itself.

In placebo-controlled trials, metformin’s ability to lower HbA1c is similar to that of SUs (ie, −1% to 2%, placebo-adjusted) (Table 1). When compared with SUs in head-to-head trials, metformin’s glucose-lowering effect is generally equivalent (Table 2). Metformin monotherapy, however, is associated with weight loss (or no weight gain) and much less hypoglycemia than SU therapy. Because of the lack of beta cell stimulation, circulating insulin concentrations tend to decline, which may provide a cardiovascular advantage. Other nonglycemic benefits have also been ascribed to metformin, such as decreases in lipid levels (low-density lipoprotein cholesterol and triglycerides) and the antifibrinolytic factor plasminogen activator inhibitor 1. Recently, an amelioration in vascular reactivity or endothelial function has also been demonstrated. The only study that has examined the overall effectiveness of metformin on long-term complications is the UKPDS, where the agent was included in the randomization schema with conventional diet therapy and intensive SU-insulin treatment in a subgroup of overweight patients. Those who received metformin experienced less hypoglycemia and weight gain than those who received SUs or insulin. With a similar HbA1c reduction observed in the other intensively treated subjects, more impressive risk reduction was noted in the primary aggregate end points. Metformin-treated subjects, for instance, had a 32% reduction in any diabetes-related end point (P = .02), 42% less diabetes-related deaths (P = .02), and a 36% reduction in all-cause mortality (P = .01). Specifically, compared with that of the conventional group, the risk of myocardial infarction was reduced by 39% (P = .01); of all macrovascular end points, by 30% (P = .02). Individual and total microvascular end points were not significantly reduced, however, presumably because of the relatively small sample size, since there were no differences in microvascular outcomes between the metformin and the SU-insulin-treated groups. These important findings suggested that the manner in which glucose levels are lowered by antidiabetic agents might uniquely influence certain outcomes. In addition, metformin has been shown to improve ovulatory function in insulin-resistant women with polycystic ovarian syndrome and, most recently, to decrease the progression from IGT to type 2 DM.

Adverse effects of metformin therapy include gastrointestinal distress, such as abdominal pain, nausea, and diarrhea, in up to 50% of patients. The frequency of these adverse effects can be minimized with food consumption and slow titration of dose; the need to discontinue therapy is uncommon. The optimal dosage in most patients appears to be 2000 mg/d. The risk of lactic acidosis is approximately 100 times less than that with phenformin therapy: approximately 1 in every 30000 patients. The drug must be avoided in those who are at increased risk for lactic acidosis, such as those with renal impairment (serum creatinine level ≥1.5 mg/dL [132.6 µmol/L] for men or ≥1.4 mg/dL [123.8 µmol/L] for women), in whom metformin clearance is diminished. Other contraindications include hepatic dysfunction, congestive heart failure, metabolic acidosis, dehydration, and alcoholism. It should be temporarily withheld in patients with virtually any acute illness and those undergoing surgery or radiographic studies. The need for additional therapies after several years of use was also demonstrated in metformin-treated subjects in the UKPDS, so beta cell failure also occurs in patients who are treated with this agent. It is approved for use as monotherapy and in combination with SUs and other secretagogues, TZDs, and insulin.

**α-Glucosidase Inhibitors.** The α-glucosidase inhibitors (AGIs; eg, acarbose and miglitol) were introduced in 1996. Their mechanism of action is unique, and this is the sole drug class not targeted at a specific pathophysiological defect of type 2 DM. An enzyme in the brush border of the proximal small intestinal epithelium, α-glucosidase serves to break down disaccharides and more complex carbohydrates. By the competitive inhibition of this enzyme, the AGIs delay intestinal carbohydrate absorption and mitigate postprandial glucose excursions.

The efficacy of AGIs is considerably less than that of either SUs or metformin, with an average HbA1c lowering effect of approximately 0.5% to 1% compared with that of placebo-treated subjects (Table 1). Not surprisingly, their greatest effect is on postprandial glucose levels, whereas the effect on fasting blood glucose levels is small. In a comparative study, acarbose had about half the glucose-lowering effect of an SU, tolbutamide. Several other head-to-head trials have claimed efficacy equal to that of SUs and metformin, but in 2 of these, the dose of the comparator drug was suboptimal (Table 2). The AGIs are attractive in that they are essentially nonsystemic and unas-
associated with hypoglycemia and weight gain. Nonglycemic benefits include small reductions in triglycerides and postprandial insulin levels.\(^9\),\(^8\) The targeting of postprandial glucose may provide a theoretical advantage because postprandial hyperglycemia has been linked with cardiovascular mortality.\(^7\) However, there have been no studies that have examined long-term effectiveness of these agents in reducing chronic complications. In addition, other classes of antidiabetic drugs reduce overall glucose levels, including those in the postprandial period.

Adverse effects of AGIs include flatulence, abdominal discomfort, and diarrhea, frequently leading to discontinuation of the drug. The AGIs are rarely used as monotherapy because of their comparatively mild efficacy. They are approved for use as monotherapy and in combination with SUs. One caveat regarding AGI therapy (specifically, when combined with secretagogues or insulin) is the requirement that hypoglycemia be reversed by consuming glucose itself, as opposed to more complex carbohydrates.

### Thiazolidinediones

In 1997, troglitazone, a TZD, was introduced in the United States. It was later removed from the market because of rare idiosyncratic hepatocellular injury.\(^8\) This novel class of drugs, currently represented by rosiglitazone and pioglitazone, has a

<table>
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<th>Source, y</th>
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<td>15 mo</td>
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<td>Dills and Schneider,(^36) 1996</td>
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<td>Birkeland et al,(^35) 1994</td>
<td>Glipizide vs glyburide</td>
<td>46</td>
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<td>Rosenstock et al,(^33) 1992</td>
<td>Glipizide vs glyburide</td>
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<td>Kilo et al,(^32) 1992</td>
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<td>Campbell et al,(^61) 1994</td>
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<td>Clarke and Campbell,(^62) 1977</td>
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<td>1 y</td>
<td>Equivalent efficacy</td>
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#### α-Glucosidase Inhibitors

| Hoffmann and Spengler,\(^57\) 1997 | Acarbose vs metformin | 96 | 24 wk | Equivalent efficacy, but metformin dose less than maximal at 850 mg twice daily |
| Segal et al,\(^83\) 1997 | Miglitol vs glibenclamide | 119 | 24 wk | Glibenclamide more efficacious than miglitol (hemoglobin A\(_1c\) −1.0% vs −0.8% [\(P\) value not reported]), but mean glibenclamide dose less than maximal at 3.6 mg/d |
| Hoffmann and Spengler,\(^84\) 1994 | Acarbose vs glibenclamide | 96 | 24 wk | Equivalent efficacy, but mean glibenclamide dose less than maximal at 4.3 mg/d |

#### Thiazolidinediones

| Kirk et al,\(^103\) 1999 | Troglitazone vs metformin (in SU-treated patients) | 32 | 14 wk | Equivalent efficacy |
| Inzucchi et al,\(^102\) 1998 | Troglitazone vs metformin | 28 | 3 mo | Equivalent efficacy |
| Horton et al,\(^104\) 1998 | Troglitazone vs glyburide | 552 | 1 y | Equivalent efficacy |

#### Non-SU Secretagogues

| Horton et al,\(^105\) 2000 | Nateglinide vs metformin | 701 | 24 wk | Metformin more effective than nateglinide (−0.3% hemoglobin A\(_1c\)) |
| Raskin et al,\(^103\) 2000 | Repaglinide vs troglitazone | 256 | 22 wk | Repaglinide more effective than troglitazone (hemoglobin A\(_1c\) −0.8% vs −0.4% [\(P<.05\)]) |
| Marbury et al,\(^106\) 1999 | Repaglinide vs glyburide | 576 | 12 mo | Equivalent efficacy |
| Landgraf et al,\(^107\) 1999 | Repaglinide vs glibenclamide | 195 | 14 wk | Equivalent efficacy |
| Wolffensbutel and Landgraf,\(^108\) 1999 | Repaglinide vs glyburide | 424 | 1 y | Equivalent efficacy |

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TZDs currently available, rosiglitazone and pioglitazone, appear to have similar efficacy on glycemia. Adverse effects of TZDs include weight gain, which can be as great or greater than that with the SUs. Weight gain appears to involve mostly peripheral subcutaneous sites, with a reduction in visceral fat depots, the latter being better correlated with insulin resistance. Edema can also occur. Both weight gain and edema are more common in patients who receive TZDs with insulin. Anemia may also occur infrequently. Although the Food and Drug Administration still recommends periodic measurement of hepatic function, the available TZDs, unlike troglitazone, have not been convincingly associated with liver injury. Patients with advanced forms of congestive heart failure and those with hepatic impairment should not receive TZDs. Thiazolidinediones are the most expensive class of antidiabetic medication and are indicated as monotherapy and in combination with metformin, SUs, and insulin (pioglitazone only).

Non-SU Secretagogues. The mechanism of action of the non-SU insulin secretagogues (repaglinide [a benzoic acid derivative] and nateglinide [a phenylalanine derivative]) is similar to that of SUs: interaction with voltage-dependent K$_{ATP}$ channels on beta cells. They are distinguished from the SUs by their short metabolic half-lives, which result in brief episodic stimulation of insulin secretion. There are 2 important consequences from this difference. First, postprandial glucose excursions are attenuated because of greater insulin secretion immediately after meal ingestion. Second, because less insulin is secreted several hours after the meal, there is decreased risk of hypoglycemia during this late postprandial phase. One agent, nateglinide, has little stimulatory effect on insulin secretion when administered in the fasting state. Thus, nateglinide may enhance meal-stimulated insulin secretion more than other secretagogues do. Efficacy of repaglinide is similar to that of SUs.
whereas nateglinide appears to be somewhat less potent a secretagogue (Table 1).128 Three comparative trials129-131 (Table 2) of repaglinide vs SU have been published, each showing equal lowering of glucose levels. In single studies, the efficacy of repaglinide was equal to that of metformin132 but greater than that of troglitazone.133 In 1 study, nateglinide was less efficacious than metformin.134 These drugs have not been assessed for their long-term effectiveness in decreasing microvascular or macrovascular risk. Adverse effects include hypoglycemia and weight gain, which are probably less pronounced than that caused by the SUs.129 One disadvantage of this drug category is the frequent dosing schedule required with meals. Repaglinide and nateglinide are hepatically metabolized and renally cleared and should be use cautiously when function of the liver and kidneys is impaired. They are approved for use either as monotherapy or in combination with metformin.

**Monotherapy Recommendations**

Given the myriad therapeutic options available for type 2 DM, how does the physician choose the best drug for a specific patient? Except for the AGIs and nateglinide, which are generally less effective, each of the other drugs will lead to a similar reduction in HbA1c. TABLE 3 summarizes the relative advantages and disadvantages of different drug classes. Does one drug class hold an advantage over the others? Because metformin is the only drug associated with weight loss, or at least weight neutrality, it has become the most widely prescribed single antihyperglycemic drug and is generally regarded as the best first-line agent, at least in the obese patient without contraindications for its use. Its favorable performance in the UKPDS58 supports this approach. In addition, the virtual lack of hypoglycemia makes metformin therapy an attractive option, particularly in patients whose control is approaching the euglycemic range.

The precise role for the insulin secretagogues is evolving. Their association with hypoglycemia and weight gain remains problematic, and concerns regarding hyperinsulinemia and beta cell exhaustion persist. Although cost-effective in terms of glucose lowering effect, these agents are being used less as first-line therapy. They remain an important element of combination regimens. Even in an era with increasing emphasis on the role of insulin resistance in type 2 DM, insulin deficiency remains a critical pathophysiological

### Table 3. Currently Available Oral Therapeutic Options for Type 2 Diabetes Mellitus

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<td>Hypoglycemia</td>
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<td>Weight gain</td>
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<tr>
<td>Hyperinsulinemia (role uncertain)</td>
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<tr>
<td>More complex (3 times daily) dosing schedule</td>
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<td>Adverse gastrointestinal effects</td>
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<td>More complex (3 times daily) dosing schedule</td>
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<tr>
<td>Liver function test monitoring</td>
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<td>Weight gain</td>
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<tr>
<td>Edema</td>
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<tr>
<td>Slow onset of action</td>
<td></td>
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<tr>
<td>No long-term data</td>
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<td>No long-term data</td>
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### Food and Drug Administration approval status

| Monotherapy | Combination with insulin, metformin, thiazolidinedione, α-glucosidase inhibitors |
| Monotherapy | Combination with metformin |
| Monotherapy | Combination with insulin, SU, non-SU secretagogue, thiazolidinedione |
| Monotherapy | Combination with SU |
| Monotherapy | Combination with insulin (pioglitazone only), SU, metformin |
target of therapy. In addition, some consider them the best first-line agents in nonobese patients who have type 2 DM and may exhibit more pancreatic secretory dysfunction than insulin resistance. Although metformin’s benefits in reducing cardiovascular end points were demonstrated solely in overweight patients in the UKPDS, its effect on lowering glucose levels is not predicted by body weight. (In general, the predictors of response to other drug classes have not been well studied. In a meta-analysis, the best responders to TZD therapy had the highest C-peptide concentrations, suggesting greater insulin resistance, more preserved beta cell function, or both.)

The niche for the non-SU secretagogues is also unclear. They may be preferred in those who require secretagogue therapy and have irregular meal schedules. However, their use must be balanced with their increased cost compared with the now generic SUs and a considerably less convenient dosing schedule.

Although the TZDs are interesting compounds of great promise, there are no long-term data on microvascular or macrovascular risk. One may presume that any agent that lowers glucose levels will eventually lead to a similar microvascular risk reduction as other agents. Indeed, long-term studies of the impact of the newer agents on microvascular end points are unlikely, given the now accepted benefit of conventional agents in this regard. An effect on macrovascular disease is more difficult to predict because of the lack of convincing data that this disease is necessarily associated solely with glucose-level control. Evidence is mounting for an antiatherosclerotic potential for the TZDs, but because of their increased cost, the continued requirement for liver function test monitoring, and the potential for weight gain and edema, they are not widely considered the ideal monotherapy choice. Somewhat paradoxically, TZDs appear to be most effective when used with the earliest forms of diabetes, such as in the drug-naive patient when insulin secretion is still substantial. As more data emerge regarding beta cell preservation, which may be a unique benefit of this class, and cardiovascular risk reduction, the TZDs or similar drugs may one day emerge as the best first-line agent for diabetes. However, unlike other agents, TZDs may take weeks or sometimes months to exert their full glycemic effect. Therefore, they are less attractive when rapid lowering of glucose levels is desired.

In summary, in terms of antihyperglycemic effect alone, there is no compelling reason to favor one of the major categories of antidiabetic agents (SUs, biguanides, and TZDs) over another. However, metformin’s performance in the UKPDS in obese patients, ie, its lack of associated hypoglycemia and weight gain, make it the most attractive option for obese—if not all—patients who have type 2 DM but no contraindications for its use. The emerging TZD class may provide for additional cardiovascular protection for type 2 DM patients, but TZDs’ cost and adverse-effect profile make them less fitting as monotherapy, unless metformin is contraindicated or poorly tolerated. The actual choice of a drug, however, must be based on a variety of clinical factors and individual patient characteristics, including predisposition to adverse effects, the degree of hyperglycemia, and cost. The paramount concern of the physician should be attainment of the best glycemic control with whatever antidiabetic regimen is well tolerated.

Combination Therapy

Given the multiple pathophysiologic lesions in type 2 DM, combination therapy is a logical approach to its management. The UKPDS clearly demonstrated that type 2 DM is a progressive disease. After 3 years, for example, type 2 DM in only 50% of patients was adequately controlled with a single drug, and after 9 years, this percentage had decreased to 25%. Each clinical trial that has examined the addition of an oral agent to that of another class has demonstrated additive HbA1c reduction (Table 4). With few exceptions, the effect on HbA1c has been similar to the effect from using the added drug as monotherapy vs placebo. The most popular combinations are SU and metformin, metformin and TZD, and SU and TZD. Triple combination therapy, typically SU, metformin, and TZD, improved glycemia in 1 placebo-controlled study but is not formally approved by the Food and Drug Administration. Since HbA1c reduction is the overriding goal in all patients, the precise combination used may not be as important as the glucose levels achieved. There is no evidence that a specific combination is any more effective in lowering glucose levels or more effective in preventing complications than another. So the same patient-specific criteria that go into the decision tree for monotherapy apply when more complex regimens are constructed. In the UKPDS, however, a group of patients who did not achieve acceptable control with SU therapy was randomized to the early addition of metformin. The results of this sub-study were somewhat unexpected in that combination therapy was associated with a 96% increase in diabetes-related mortality. The authors performed an epidemiological analysis on all subjects who received this combination, and overall, no increased risk was shown. Because a deleterious effect of such a commonly used combination is not biologically plausible, avoiding the combination is not recommended. In fact, a fixed combination tablet containing glyburide and metformin has recently become available. Combination therapy involving 2 or 3 drug classes with distinct mechanisms of action will not only improve glycemic control, but also result in lower overall drug dosing in some settings and minimize adverse effects. If glycemic control cannot be attained with oral agents alone, there should be no hesitation about using insulin either alone or in combination with oral agents. The latter approach may be preferred, since it leads to im-
proved glycemic control and a lower insulin dose compared with insulin monotherapy.

**COMMENT**

Type 2 diabetes mellitus is a complex disorder associated with significant health and economic burdens. Keeping blood glucose levels near the normal range lowers the risk of complications and is an important therapeutic goal. A number of oral antihyperglycemic agents have been introduced in the United States during the past several years, each with its own mode of action. They are equally effective in lowering blood glucose concentrations and HbA1c, except for the AGIs and nateglinide, which in general appear to be less potent. Only SUs and metformin have been shown to reduce microvascular complications, with metformin exhibiting additional benefits on macrovascular risk. Because they lower glucose levels, however, the remaining drug classes will presumably have a proportionate effect on microvascular complications. Their effect on macrovascular risk, however, remains unknown. The proper choice of antidiabetic agent for a patient is based on several factors. Each drug class has unique adverse effects and prescribing precautions. The popularity of insulin sensitizers, defined broadly as metformin and TZDs, is increasing, since these agents avoid the risk of hypoglycemia associated with secretagogue therapy and allow for the treatment of patients already near the euglycemic range. Most patients will require combination therapy as their disease progresses.

**Table 4. Antidiabetic Oral Agent Combination Therapy: Randomized Controlled Trials**

<table>
<thead>
<tr>
<th>Source, y</th>
<th>Randomization</th>
<th>Subject No.</th>
<th>Study Length</th>
<th>Hemoglobin A1c Reduction, %†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Erle et al,140 1999</td>
<td>Glyburide + metformin vs glyburide + placebo</td>
<td>40</td>
<td>6 mo</td>
<td>1.0</td>
</tr>
<tr>
<td>UKPDS,19 1998</td>
<td>SU + metformin vs SU alone</td>
<td>591</td>
<td>3 y</td>
<td>0.6</td>
</tr>
<tr>
<td>DeFronzo and Goodman,52 1995</td>
<td>Glyburide + metformin vs glyburide alone</td>
<td>632</td>
<td>29 wk</td>
<td>1.6</td>
</tr>
<tr>
<td>Standl et al,146 2001</td>
<td>Metformin/glyburide + miglitol vs metformin/glyburide + placebo</td>
<td>154</td>
<td>24 wk</td>
<td>0.4</td>
</tr>
<tr>
<td>Wilms and Ruge,145 1999</td>
<td>SU + acarbose vs SU + metformin vs SU + placebo</td>
<td>89</td>
<td>12 wk</td>
<td>1.0 (+ acarbose), 1.2 (+ metformin)</td>
</tr>
<tr>
<td>Holman et al,141 1999</td>
<td>Variety of treatments + acarbose vs variety of treatments + placebo</td>
<td>973</td>
<td>3 y</td>
<td>0.2</td>
</tr>
<tr>
<td>Rosenstock et al,142 1998</td>
<td>Metformin + acarbose vs metformin + placebo</td>
<td>148</td>
<td>24 wk</td>
<td>0.7</td>
</tr>
<tr>
<td>Scopiglione et al,143 1999</td>
<td>Variety of treatments + acarbose vs variety of treatments + placebo</td>
<td>250</td>
<td>12 mo</td>
<td>0.1 (P = NS)</td>
</tr>
<tr>
<td>Johnston et al,84 1994</td>
<td>SU + miglitol vs SU + placebo</td>
<td>192</td>
<td>14 wk</td>
<td>0.8</td>
</tr>
<tr>
<td>Costa and Pinol,141 1997</td>
<td>Glibenclamide + acarbose vs glibenclamide + placebo</td>
<td>65</td>
<td>6 mo</td>
<td>0.8</td>
</tr>
<tr>
<td>Coniff et al,81 1995</td>
<td>Tolbutamide + acarbose vs either drug alone</td>
<td>290</td>
<td>24 wk</td>
<td>0.4 (vs tolbutamide), 0.8 (vs acarbose) Note: acarbose dose 200 mg 3 times daily (above Food and Drug Administration maximum)</td>
</tr>
<tr>
<td>Chiasson et al,74 1994</td>
<td>Metformin or SU + acarbose vs metformin or SU + placebo</td>
<td>354</td>
<td>1 y</td>
<td>0.8 to 0.9</td>
</tr>
<tr>
<td>Yale et al,150 2001</td>
<td>Metformin + SU + troglitazone vs metformin + SU + placebo</td>
<td>200</td>
<td>1 y</td>
<td>1.4</td>
</tr>
<tr>
<td>Einhorn et al,150 2000</td>
<td>Metformin + pioglitazone vs metformin + placebo</td>
<td>328</td>
<td>16 wk</td>
<td>0.8</td>
</tr>
<tr>
<td>FONSECA et al,58 2000</td>
<td>Metformin + rosiglitazone vs metformin + placebo</td>
<td>348</td>
<td>26 wk</td>
<td>1.2</td>
</tr>
<tr>
<td>Wolffensburger et al,117 2000</td>
<td>SU + rosiglitazone vs SU + placebo</td>
<td>574</td>
<td>26 wk</td>
<td>1.0</td>
</tr>
<tr>
<td>Buysschaert et al,149 1999</td>
<td>SU + troglitazone vs SU + placebo</td>
<td>259</td>
<td>16 wk</td>
<td>0.2, but troglitazone dose only 200 mg/d</td>
</tr>
<tr>
<td>Horton et al,131 1998</td>
<td>Glyburide + troglitazone vs either drug alone</td>
<td>552</td>
<td>1 y</td>
<td>2.7</td>
</tr>
<tr>
<td>Iwamoto et al,147 1996</td>
<td>SU + troglitazone vs SU + placebo</td>
<td>291</td>
<td>12 wk</td>
<td>0.9</td>
</tr>
<tr>
<td>Raskin et al,147 2000</td>
<td>Troglitazone + repaglinide vs either drug alone</td>
<td>256</td>
<td>22 wk</td>
<td>1.3 vs troglitazone, 0.9 vs repaglinide</td>
</tr>
<tr>
<td>Moses et al,132 1999</td>
<td>Metformin + repaglinide vs either drug alone</td>
<td>83</td>
<td>3 mo</td>
<td>1.1 vs metformin, 1.0 vs repaglinide</td>
</tr>
<tr>
<td>Horton et al,134 2000</td>
<td>Metformin + nateglinide vs either drug alone</td>
<td>701</td>
<td>24 wk</td>
<td>0.6 vs metformin, 0.9 vs nateglinide</td>
</tr>
</tbody>
</table>

*SU indicates sulfonylureas.
†Unless otherwise indicated, values represent the absolute percent reduction in hemoglobin A1c of combination therapy vs monotherapy.

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ORAL ANTICYSTHYLMIC THERAPY FOR TYPE 2 DIABETES

REFERENCES

73. Johansen K. Efficacy of metformin in the treat-

74. Campbell IW. Comparison of metformin and
and safety of low and high doses. Acta Diabetol.

75. Clarke BC, Campbell IW. Comparison of metfor-
m and chlorpropamide in non-obese, matura-
tion-onset diabetes untreated by diet. BMJ. 1977;2:

76. Mather KJ, Verma S, Anderson TJ. Improved en-
doehthal function with metformin in type 2 diabetes.

77. Turner RC. The U.K. Prospective Diabetes Study:

78. Lebovitz HE. a-Glucosidase inhibitors as agents

79. Santeusanio F, Ventura MM, Contandini S, Com-
pagnucci F, Moriconni V, Zaccarini P. Efficacy and
safety of two different doses of acarbose in non-
insulin-dependent diabetes mellitus: a placebo-
controlled double-blind study. Diabetes Med. 1993;10:

80. Sankuricka MJ, Flesher M, Schulze J, et al. Therapeu-
tic potentials of acarbose as first-line drug in NIDDM insuffi-
ciently treated with diet alone. Diabetes Care.

81. Chiasson JL, Josse RG, Hunt JA, et al. The ef-
cacy of acarbose in the treatment of patients with non-
insulin-dependent diabetes mellitus: a multicenter con-
trolled clinical trial. Ann Intern Med. 1994;121:928-
935.

82. Coniff RF, Shapiro JA, Seaton TB, Bray GA. Mul-
ticenter, placebo-controlled trial comparing acarbose
with placebo, tolbutamide, and tolbutamide-plus
acarbose in non-insulin-dependent diabetes mellitus.

83. Segal P, Feig P, Schemtheran G, et al. The ef-
glucigenes and safety of miglitol therapy compared with

84. Johnsen K. Efficacy of metformin in the treat-

85. Donahue RP, Abbott RD, Reed DM, Yano K. Efficacy

86. Imano E, Kanda T, Nakatani Y, et al. Effect of
troglitazone on blood concentrations of plas-
minogen activator inhibitor 1 in patients with type 2

87. 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. Dia-
pies 2001;26:1642-1649.

88. segal p, feig P, schemtheran g, et al. The ef-
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89. Donahue RP, Abbott RD, Reed DM, Yano K. Efficacy

90. Johnsen K. Efficacy of metformin in the treat-

91. Coniff RF, Shapiro JA, Seaton TB. Bray GA. Mul-
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92. Segal P, Feig P, Schemtheran G, et al. The ef-
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93. Coniff RF, Shapiro JA, Seaton TB, Bray GA. Mul-
ticenter, placebo-controlled trial comparing acarbose
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acarbose in non-insulin-dependent diabetes mellitus. 

94. Fosseva VA, Valquett TR, Huang SM, Ghazi MN, Vennie RW. Troglitazone improves glycemic control in pa-

95. Donahue RP, Abbott RD, Reed DM, Yano K. Efficacy

96. Lebovitz HE, Dole JP, Patwardhan R, Rappaport EB, Salzman A. The Rosiglitazone Clini-
ical Trials Study Group: once- and twice-daily rosi-

97. Beinlich K, Pfitzmann A, Mathiesen ES, Schneider RL. Rosiglitazone improved glycemic control in pa-

98. Gubbi A, Fleming GA. Lactic acidosis in patients with
non-insulin-dependent diabetes mellitus: efficacy and
safety of metformin and tro-

99. Coniff RF, Shapiro JA, Seaton TB, Bray GA. Mul-
ticenter, placebo-controlled trial comparing acarbose
with placebo, tolbutamide, and tolbutamide-plus
acarbose in non-insulin-dependent diabetes mellitus.

100. Imano E, Kanda T, Nakatani Y, et al. Effect of
troglitazone on blood concentrations of plas-
minogen activator inhibitor 1 in patients with type 2

ffects of troglitazone on blood glucose levels in pa-
tients with type 2 diabetes mellitus. Drugs, 2000;60:1017-1028.


103. Ginsberg H, Tylus J, Sobel BE. A review of meta-
and cardiovascular effects of oral antidiabetic
agents: beyond glucose-level lowering. J Cardiovasc

104. Lebovitz HE. a-Glucosidase inhibitors as agents
132-145.

105. 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, but not for the hypophylic effect of thiazolidinediones. J Clin Invest.

106. Imano E, Kanda T, Nakatani Y, et al. Effect of
troglitazone on blood concentrations of plas-
minogen activator inhibitor 1 in patients with type 2

107. Campbell IW. Antidiabetic drugs present and fu-
ture: will improving insulin resistance benefit cardio-
vascular risk in type 2 diabetes mellitus? Drugs, 2000;
60:1017-1028.

108. Parulkar AA, Pendergrass ML, Granda-Araya A, Lee TR, Fonseca VA. Nonhypoglycemic effects of thia-

109. Fosseva V, Rosenstock J, Patwardhan R, Salzman A. Effect of metformin and rosiglitazone combi-
nation therapy in patients with type 2 diabetes mellitus:
randomized controlled trial. JAMA. 2000;283:
1695-1702.

110. Nakano L, Judvik B, Beerdson P, Joyce M, Olfels J. Improvement in glucose tolerance and insulin re-
sistance in obese subjects treated with troglitazone. 

111. Sunayama S, Watanabe Y, Ohmura H, et al. Ef-
fects of troglitazone on blood glucose levels in pa-
tients with type 2 diabetes mellitus. Drugs, 2000;
60:1017-1028.

112. Sung BH, Izzo JJ, Dansona P, Wilson MF. Va-
sidilatory effects of troglitazone improve blood pres-
sure at rest and during mental stress in type 2 dia-

113. Kruysinska YT, Yu IG, Olfelsky JM, Sobel BE. Ef-
effects of troglitazone on blood concentrations of plas-
minogen activator inhibitor 1 in patients with type 2 
diabetes and in lean and obese normal subjects. Dia-

R666.

115. Hsu WC, Jackson S, Law RE. Control of vas-
cular cell proliferation and migration by PPAR-gamma:

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