Oral Antihyperglycemic Therapy for Type 2 Diabetes

Scientific Review

Silvio E. Inzucchi, MD

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 A_{1c} was reported. When multiple dosages of a drug were tested, the results of the highest approved dosage were used. In placebo-controlled trials, hemoglobin A_{1c} 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 A_{1c} 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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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 increases 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.[5-7] 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.

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

Author Affiliation: Section of Endocrinology, Yale University School of Medicine, New Haven, Conn.
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Corresponding Author and Reprints: Silvio E. Inzucchi, MD, Endocrinology, TMP 534, Yale School of Medicine, Box 208020, New Haven, CT 06520 (e-mail: silvio.inzucchi@yale.edu).
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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 A_{1c} (HbA_{1c}) reported. When multiple doses of a drug were tested, the results of the highest approved dose were used. In placebo-controlled trials, HbA_{1c} 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.[8,9] 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[9,10] and is detected in normoglycemic first-degree relatives of patients with type 2 DM.[11-13] 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.[14] They are said to have the metabolic syndrome,[15] 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.[16]

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 dampens the insulin response in skeletal muscle[17,18] while further impairing pancreatic insulin secretion as well as augmenting hepatic glucose production ("lipotoxicity").[19]

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 HbA_{1c} level of less than 7%.[20] More stringent guidelines[21] 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 HbA_{1c} levels at 6.5%. These recommendations are based on findings from 3 landmark studies: the Diabetes Control and Complications Trial,[5] the Kumamoto Study,[6] and the United Kingdom Prospective Diabetes Study (UKPDS),[7] 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 also they 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]

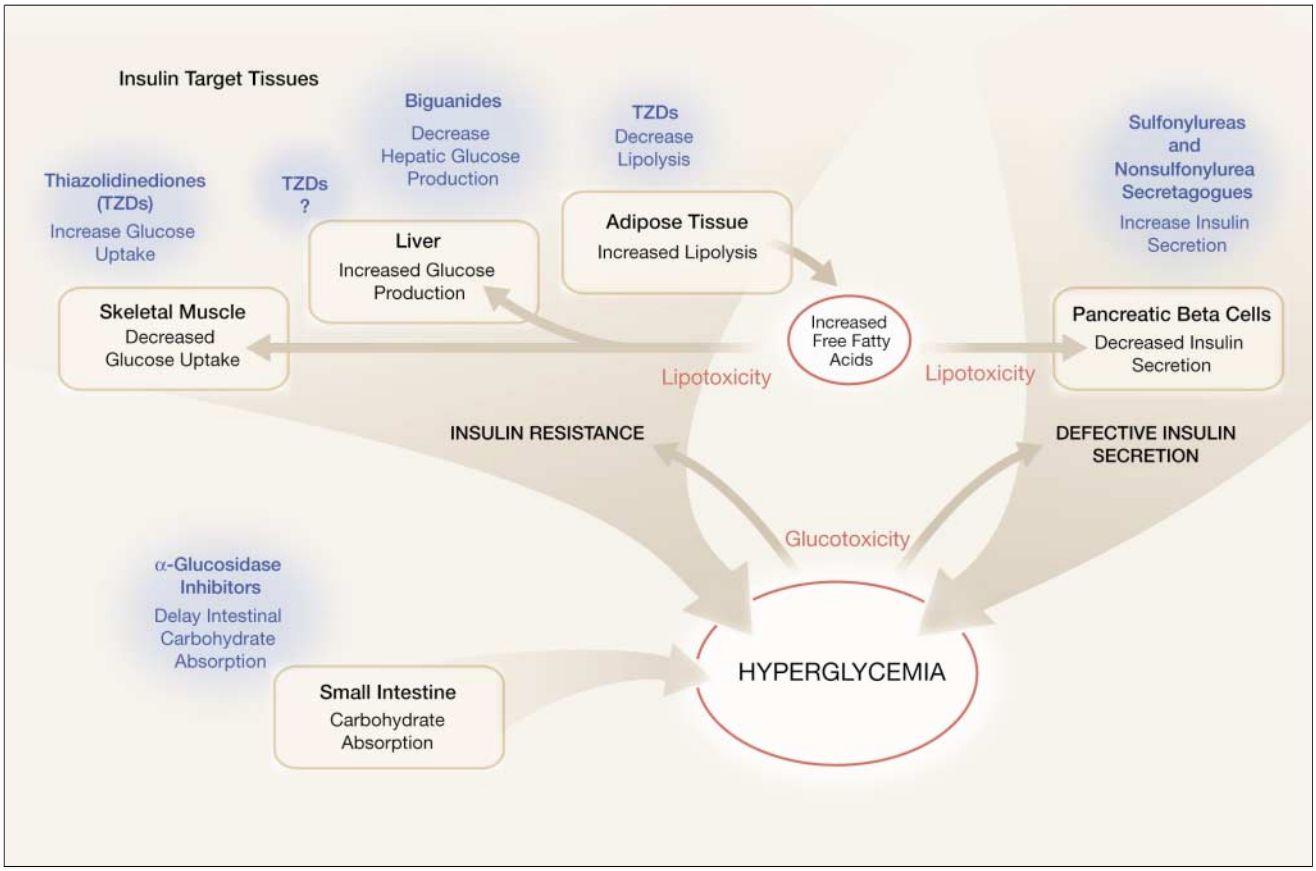
Pharmacological Therapy

Sulfonylureas. Sulfonylurea (SU) drugs have been available in the United States since 1954. Second-generation SUs (glyburide, glipizide, and glimepiride) are more potent and probably safer than first-generation SUs (chlorpropamide, tolbutamide, acetohexamide, and tolazamide) but essentially of equal efficacy.[24] 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_{ATP}) channels, facilitating cell membrane depolarization, calcium entry into the cell, and insulin secretion.[25] 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.[26] 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.[27,28] 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_{1c} of approximately 1% to 2% (TABLE 1).[7,29,30] One study[31] demonstrated a more impressive change, but the rise in HbA_{1c} level experienced by the placebo group was greater than usual, reaching 2%. Current agents are equally efficacious[32-37] 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_{ATP} channels similar to those of beta cells. Glimepiride, therefore, may reduce ischemic preconditioning less than the other SUs do,[38] 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.[39,40] An early trial by the University Group Diabetes Project,[41] which explored the effectiveness of oral agents vs insulin, found increased cardiovascular mortality in the cohort of patients randomized to SUs. Widespread criticism of the project's methodology has placed the validity of its findings in doubt.[42] In the more recent UKPDS, which had a better experimental design, increased mortality was not shown in SU-treated subjects.[7] Given these agents' 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

Figure. Pharmacological Approaches to the Major Metabolic Defects of Type 2 Diabetes Mellitus



a group of patients frequently already overweight.[7,25,28,29] The second is hypoglycemia, most likely to affect the elderly, those with worsening renal function, and those with irregular meal schedules.[7,25,32]

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 ($P=.05$).[7] 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 hyperinsulinemia.

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

Table 1. Antidiabetic Oral Agent Monotherapy: Randomized Controlled Clinical Trials*

Source, y	Treatment Arms	Subjects, No.	Study Length	Hemoglobin A_{1c} Reduction, %†
	Sulfonylureas			
UKPDS,[7] 1998	Sulfonylureas vs diet	3867	10 y	0.9
Schade et al,[29] 1998	Glimepiride vs placebo	249	22 wk	1.4
Simonson et al,[28] 1984	Glipizide GITS vs placebo	204	12 wk	1.8
Rosenstock et al,[31] 1996	Glimepiride vs placebo	416	14 wk	2.5
	Metformin			
UKPDS,[58] 1998	Meformin vs diet	753	10.7 y	0.8
Hoffmann and Spengler,[57] 1997	Metformin vs placebo	96	24 wk	1.1
Garber et al,[56] 1997	Metformin vs placebo	452	11 wk	2.0
Grant,[55] 1996	Metformin vs placebo	75	6 mo	1.7
DeFronzo and Goodman,[52] 1995	Metformin vs placebo	289	29 wk	1.5
Nagi and Yudkin,[54] 1993	Metformin vs placebo	27	12 wk	1.3
Dornan et al,[53] 1991	Metformin vs placebo	60	8 mo	3.0
	α-Glucosidase Inhibitors			
Hasche et al,[80] 1999	Acarbose vs placebo	74	24 mo	0.9
Scott et al,[79] 1999	Acarbose vs placebo	105	16 wk	0.4
Fischer et al,[77] 1998	Acarbose vs placebo	495	24 wk	1.0
Johnston et al,[78] 1998	Miglitol vs placebo	345	12 mo	0.7
Hoffmann and Spengler,[82] 1997	Acarbose vs placebo	96	24 wk	1.3
Braun et al,[76] 1996	Acarbose vs placebo	86	24 wk	0.9
Coniff et al,[75] 1995	Acarbose vs placebo	290	16 wk	0.8
Coniff et al,[81] 1995	Acarbose vs placebo	212	24 wk	0.6
Chiasson et al,[74] 1994	Acarbose vs placebo	354	1 y	0.9
Hotta et al,[71] 1993	Acarbose vs placebo	40	24 wk	1.0
Santeusanio et al,[72] 1993	Acarbose vs placebo	62	16 wk	0.6
Hanefeld et al,[70] 1991	Acarbose vs placebo	94	24 wk	0.6
	Thiazolidinediones			
Lebovitz et al,[100] 2001	Rosiglitazone vs placebo	493	26 wk	1.5
Phillips et al,[99] 2001	Rosiglitazone vs placebo	959	26 wk	1.5
Aronoff et al,[101] 2000	Pioglitazone vs placebo	408	26 wk	1.6
Fonseca et al,[98] 1998	Troglitazone vs placebo	402	6 mo	1.1
	Non-SU Secretagogues			
Jovanovic et al,[126] 2000	Repaglinide vs placebo	93	6 mo	1.9
Horton et al,[134] 2000	Nateglinide vs placebo	701	24 wk	1.0
Hanefeld et al,[128] 2000	Nateglinide vs placebo	289	12 wk	0.6
Goldberg et al,[127] 1998	Repaglinide vs placebo	99	18 wk	1.7

*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.[30,43] 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.[44] An earlier biguanide, phenformin, was removed from the market in the 1970s because of an association with lactic acidosis.[45] In contrast to the SUs, metformin does not stimulate insulin secretion.[46,47] 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.[48,49] It is therefore considered an insulin sensitizer. Increased peripheral glucose disposal has also been measured,[44,50] although this is most likely a secondary phenomenon caused by lowering of glucotoxicity and not a direct effect of the drug itself.[48,51]

In placebo-controlled trials, metformin's ability to lower HbA_{1c} is similar to that of SUs (ie, –1% to 2%, placebo-adjusted) (Table 1).[52-59] When compared with SUs in head-to-head trials, metformin's glucose-lowering effect is generally equivalent (**TABLE 2**).[60-63] Metformin monotherapy, however, is associated with weight loss (or no weight gain) and much less hypoglycemia than SU therapy.[44,47,48] 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)[52,64] and the antifibrinolytic factor plasminogen activator inhibitor 1.[64] Recently, an amelioration in vascular reactivity or endothelial function has also been demonstrated.[65] 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 HbA_{1c} 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% ($P=.02$).[58] 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.[44] 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.[56] The risk of lactic acidosis is approximately 100 times less than that with phenformin therapy: approximately 1 in every 30 000 patient-years.[66] 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 radiocontrast 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.[67] 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.[68,69]

The efficacy of AGIs is considerably less than that of either SUs or metformin, with an average HbA_{1c} lowering effect of approximately 0.5% to 1% compared with that of placebo-treated subjects (Table 1).[57,70-80] Not surprisingly, their greatest effect is on postprandial glucose levels, whereas the effect on fasting blood glucose levels is small.[57,70-80] In a comparative study, acarbose had about half the glucose-lowering effect of an SU, tolbutamide.[81] Several other head-to-head trials have claimed efficacy equal to that of SUs[82,83] and metformin,[57] but in 2 of these,[57,82] the dose of the comparator drug was suboptimal (Table 2).

The AGIs are attractive in that they are essentially nonsystemic and unas-

sociated with hypoglycemia and weight gain. Nonglycemic benefits include small reductions in triglycerides and postprandial insulin levels.[69,84] The targeting of postprandial glucose may provide a theoretical advantage because postprandial hyperglycemia has been linked with cardiovascular mortality.[85] 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.[86] This novel class of drugs, currently represented by rosiglitazone and pioglitazone, has a

Table 2. Antidiabetic Oral Agent Monotherapy: Randomized Head-to-Head Trials*

Source, y	Treatment Arms	Subjects, No.	Study Length	Hemoglobin A_{1c} Results
		Sulfonylureas		
Kitbachi et al,[37] 2000	Glipizide vs glyburide	18	15 mo	Equivalent efficacy
Dills and Schneider,[36] 1996	Glimepiride vs glyburide	577	1 y	Equivalent efficacy
Birkeland et al,[35] 1994	Glipizide vs glyburide	46	15 mo	Equivalent efficacy
Carlson et al,[34] 1993	Glyburide vs micronized glyburide	206	12 wk	Equivalent efficacy
Rosenstock et al,[33] 1993	Glipizide vs glyburide	139	4 mo	Equivalent efficacy
Kilo et al,[32] 1992	Glipizide vs glyburide	34	3 mo	Equivalent efficacy
		Metformin		
Tessier et al,[60] 1999	Metformin vs gliclazide	36	24 wk	Equivalent efficacy
UKPDS,[58] 1998	Meformin vs various SUs	753	10.7 y	Equivalent efficacy
Campbell et al,[61] 1994	Metformin vs glipizide	48	1 y	Metformin more efficacious than glipizide (hemoglobin A_{1c} −2.6% vs −1.9% [$P<.05$])
Hermann,[62] 1994	Metformin vs glyburide	165	6 mo	Equivalent efficacy
Clarke and Campbell,[63] 1977	Metformin vs chlorpropamide	216	1 y	Equivalent efficacy
		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,[82] 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,[134] 2000	Nateglinide vs metformin	701	24 wk	Metformin more effective than nateglinide (−0.3% hemoglobin A_{1c})
Raskin et al,[133] 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,[129] 1999	Repaglinide vs glyburide	576	12 mo	Equivalent efficacy
Landgraf et al,[130] 1999	Repaglinide vs glibenclamide	195	14 wk	Equivalent efficacy
Wolffenbuttel and Landgraf,[131] 1999	Repaglinide vs glyburide	424	1 y	Equivalent efficacy
Moses et al,[132] 1999	Repaglinide vs metformin	83	3 mo	Equivalent efficacy

*SU indicates sulfonylurea.

unique mechanism of action that remains incompletely understood. Thiazolidinediones are pharmacological ligands for a nuclear receptor known as peroxisome-proliferator-activited receptor gamma. When activated, the receptor binds with response elements on DNA, altering transcription of a variety of genes that regulate carbohydrate and lipid metabolism.[87] The most prominent effect of TZDs is increased insulin-stimulated glucose uptake by skeletal muscle cells.[88-91] Thus, these agents decrease insulin resistance in peripheral tissues. Hepatic glucose production is decreased, although perhaps only at the highest doses.[51,90] Peroxisome-proliferator-activited receptor gamma activation also reduces lipolysis and enhances adipocyte differentiation. It is interesting to consider that the receptor is most highly expressed in adipocytes, while expression in myocytes is comparatively minor. Therefore, the increase in glucose uptake by muscle may largely be an indirect effect mediated through TZD interaction with adipocytes.[92] Candidates for the intermediary signal between fat and muscle include leptin, free fatty acids, tumor necrosis factor α, adiponectin, and the more recently isolated resistin.[93]

As with metformin, the TZDs do not stimulate pancreatic islet cells to secrete more insulin. Indeed, insulin concentrations are usually reduced, perhaps to an even greater extent than with metformin.[56,57] Thiazolidinediones enhance the responsiveness and efficiency of beta cells, presumably by decreasing glucose and free fatty acid levels, both of which have deleterious effects on insulin secretion.[94] Preliminary data also suggest that this drug class may actually prolong beta cell survival.[95,96]

In placebo-controlled trials, TZDs generally lower HbA_{1c} as much as SUs and metformin do,[97-101] and more than AGIs do (Table 1). Head-to-head studies have been performed on TZDs vs metformin[102,103] and SUs,[104] with equivalent reductions in HbA_{1c} (Table 2). No long-term outcome studies on microvascular end points are available. In relatively short-term studies, TZDs appear to lower microalbumin excretion, perhaps a manifestation of their beneficial effect on endothelial function.[100,105] Since TZDs decrease insulin resistance and because the latter is associated with macrovascular disease, some have wondered whether these drugs might provide cardiovascular protection.[38,106,107] Preliminary evidence suggests that this notion may by justified.[108]

In addition to their ability to lower insulin levels, the TZDs also have certain lipid benefits. High-density lipoprotein cholesterol concentrations, for instance, increase with TZD therapy and triglyceride concentrations frequently fall.[101,104] The effect on low-density lipoprotein cholesterol concentrations is more variable, with increases reported with some,[104,109] but not all,[101] agents. Any rise in low-density lipoprotein cholesterol concentrations may be due to a shift from small and dense to large and buoyant low-density lipoprotein particles, which are less atherogenic.[110,111]

Thiazolidinediones also slightly reduce blood pressure,[112] enhance fibrinolysis,[113] and improve endothelial function.[114] These agents also appear to decrease in vitro vascular inflammation and vascular smooth muscle cell proliferation,[115] both important elements in the atherosclerotic process. Animal data suggest an antiatherosclerotic effect.[116] However, whether such nonglycemic effects will eventually translate into benefits on actual clinical end points remains unclear. Only 3 human studies have examined more than just biochemical effects related to vascular disease. In a Japanese investigation troglitazone reduced intimal-medial thickness of carotid arteries in diabetic patients, as measured by ultrasound.[117] Similar changes were more recently reported with pioglitazone by the same group.[118] In another study, troglitazone decreased neointimal proliferation after angioplasty.[119] Several studies examining the clinical implications of these findings are under way, although data most likely will not be available for several more years. The 2 TZDs currently available, rosiglitazone and pioglitazone, appear to have similar efficacy on glycemia.[120]

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,[121] 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.[122] There are 2 important consequences from this difference. First, postprandial glucose excursions are attenuated because of greater insulin secretion immediately after meal ingestion.[123] Second, because less insulin is secreted several hours after the meal, there is decreased risk of hypoglycemia during this late postprandial phase.[124] One agent, nateglinide, has little stimulatory effect on insulin secretion when administered in the fasting state.[125] Thus, nateglinide may enhance meal-stimulated insulin secretion more than other secretagogues do. Efficacy of repaglinide is similar to that of SUs,[126,127]

whereas nateglinide appears to be somewhat less potent a secretagogue (Table 1).[128] Three comparative trials[129-131] (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 metformin[132] 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 HbA_{1c}. 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 UKPDS[58] 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

Sulfonylureas (SUs)	Non-SU Secretagogues	Biguanides	α-Glucosidase Inhibitors	Thiazolidinediones
Mechanism of action				
Increased pancreatic insulin secretion	Increased pancreatic insulin secretion	Decreased hepatic glucose production	Decreased gut carbohydrate absorption	Increased peripheral glucose disposal
Advantages				
Well established	Targets postprandial glycemia	Well established	Targets postprandial glycemia	No hypoglycemia
Decreases microvascular risk	Possibly less hypoglycemia and weight gain than with SUs	Weight loss	No hypoglycemia	Reverses prime defect of type 2 diabetes
Convenient daily dosing		No hypoglycemia	Nonsystemic	Nonglycemic benefits (decreased lipid levels, increased fibrinolysis, decreased hyperinsulinemia, improved endothelial function)
		Decreases microvascular risk		Possible beta cell preservation
		Decreases macrovascular risk		Convenient daily dosing
		Nonglycemic benefits (decreased lipid levels, increased fibrinolysis, decreased hyperinsulinemia)		
		Convenient daily dosing		
Disadvantages				
Hypoglycemia	More complex (3 times daily) dosing schedule	Adverse gastrointestinal effects	More complex (3 times daily) dosing schedule	Liver function test monitoring
Weight gain	Hypoglycemia	Many contraindications	Adverse gastrointestinal effects	Weight gain
Hyperinsulinemia (role uncertain)	Weight gain	Lactic acidosis (rare)	No long-term data	Edema
	No long-term data			Slow onset of action
	Hyperinsulinemia (role uncertain)			No long-term data
Food and Drug Administration approval status				
Monotherapy	Monotherapy	Monotherapy	Monotherapy	Monotherapy
Combination with insulin, metformin, thiazolidinedione, α-glucosidase inhibitors	Combination with metformin	Combination with insulin, SU, non-SU secretagogue, thiazolidinedione	Combination with SU	Combination with insulin (pioglitazone only), SU, metformin

target of therapy.[135,136] 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.[137] 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.[52,62] (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.)[138]

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,[39,106,107] 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,[98,101] when insulin secretion is still substantial. As more data emerge regarding beta cell preservation,[94,95] 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 contradindications 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 pathophysiological 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%.[139]

Each clinical trial that has examined the addition of an oral agent to that of another class has demonstrated additive HbA_{1c} reduction (TABLE 4).[104,132,134,140-151] With few exceptions,[104] the effect on HbA_{1c} 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[152] but is not formally approved by the Food and Drug Administration. Since HbA_{1c} 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 substudy were somewhat unexpected in that combination therapy was associated with a 96% increase in diabetes-related mortality.[58] 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[140] and minimize adverse effects. If glycemic control cannot be attained with oral agents alone, there should be no hesitation about using insulin either alone[152] or in combination[153,154] 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 HbA_{1c}, 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 unkown. 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*

Source, y	Randomization	Subject No.	Study Length	Hemoglobin A_{1c} Reduction, %†
Erle et al,[140] 1999	Glyburide + metformin vs glyburide + placebo	40	6 mo	1.0
UKPDS,[58] 1998	SU + metformin vs SU alone	591	3 y	0.6
DeFronzo and Goodman,[52] 1995	Glyburide + metformin vs glyburide alone	632	29 wk	1.6
Standl et al,[146] 2001	Metformin/glyburide + miglitol vs metformin/glyburide + placebo	154	24 wk	0.4
Willms and Ruge,[145] 1999	SU + acarbose vs SU + metformin vs SU + placebo	89	12 wk	1.0 (+ acarbose), 1.2 (+ metformin)
Holman et al,[144] 1999	Variety of treatments + acarbose vs variety of treatments + placebo	973	3 y	0.2
Rosenstock et al,[142] 1998	Metformin + acarbose vs metformin + placebo	148	24 wk	0.7
Scorpiglione et al,[143] 1999	Variety of treatments + acarbose vs variety of treatments + placebo	250	12 mo	0.1 (P = NS)
Johnston et al,[84] 1994	SU + miglitol vs SU + placebo	192	14 wk	0.8
Costa and Pinol,[141] 1997	Glibenclamide + acarbose vs glibenclamide + placebo	65	6 mo	0.8
Coniff et al,[81] 1995	Tolbutamide + acarbose vs either drug alone	290	24 wk	0.4 (vs tolbutamide), 0.8 (vs acarbose) Note: acarbose dose 200 mg 3 times daily (above Food and Drug Administration maximum)
Chiasson et al,[74] 1994	Metformin or SU + acarbose vs metformin or SU + placebo	354	1 y	0.8 to 0.9
Yale et al,[152] 2001	Metformin + SU + troglitazone vs metformin + SU + placebo	200	1 y	1.4
Einhorn et al,[150] 2000	Metformin + pioglitazone vs metformin + placebo	328	16 wk	0.8
Fonseca et al,[109] 2000	Metformin + rosiglitazone vs metformin + placebo	348	26 wk	1.2
Wolffenbuttel et al,[151] 2000	SU + rosiglitazone vs SU + placebo	574	26 wk	1.0
Buysschaert et al,[148] 1999	SU + troglitazone vs SU + placebo	259	16 wk	0.2, but troglitazone dose only 200 mg/d
Horton et al,[104] 1998	Glyburide + troglitazone vs either drug alone	552	1 y	2.7
Iwamoto et al,[147] 1996	SU + troglitazone vs SU + placebo	291	12 wk	0.9
Raskin et al,[133] 2000	Troglitazone + repaglinide vs either drug alone	256	22 wk	1.3 vs troglitazone, 0.9 vs repaglinide
Moses et al,[132] 1999	Metformin + repaglinide vs either drug alone	83	3 mo	1.1 vs metformin, 1.0 vs repaglinide
Horton et al,[134] 2000	Metformin + nateglinide vs either drug alone	701	24 wk	0.6 vs metformin, 0.9 vs nateglinide

*SU indicates sulfonylurea.
†Unless otherwise indicated, values represent the absolute percent reduction in hemoglobin A_{1c} of combination therapy vs monotherapy.

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