

# Efficacy of Glyburide/Metformin Tablets Compared with Initial Monotherapy in Type 2 Diabetes

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Many patients with type 2 diabetes fail to achieve or maintain the American Diabetes Association's recommended treatment goal of glycosylated hemoglobin levels. This multicenter, double-blind trial enrolled patients with type 2 diabetes who had inadequate glycemic control [glycosylated hemoglobin A<sub>1C</sub> (A1C), >7% and <12%] with diet and exercise alone to compare the benefits of initial therapy with glyburide/metformin tablets vs. metformin or glyburide monotherapy. Patients (n = 486) were randomized to receive glyburide/metformin tablets (1.25/250 mg), metformin (500 mg), or glyburide (2.5 mg). Changes in A1C, fasting plasma glucose, fructosamine, serum lipids, body weight, and 2-h postprandial glucose after a standardized meal were assessed after 16 wk of treatment. Gly-

buride/metformin tablets caused a superior mean reduction in A1C from baseline (-2.27%) vs. metformin (-1.53%) and glyburide (-1.90%) monotherapy (*P* = 0.0003). Glyburide/metformin also significantly reduced fasting plasma glucose and 2-h postprandial glucose values compared with either monotherapy. The final mean doses of glyburide/metformin (3.7/735 mg) were lower than those of metformin (1796 mg) and glyburide (7.6 mg). First-line treatment with glyburide/metformin tablets provided superior glycemic control over component monotherapy, allowing more patients to achieve American Diabetes Association treatment goals with lower component doses in drug-naïve patients with type 2 diabetes. (*J Clin Endocrinol Metab* 88: 3598–3604, 2003)

THE BENEFITS OF intensive glycemic control in reducing microvascular complications of type 2 diabetes have been clearly demonstrated in long-term interventional trials (1–4). However, many patients with type 2 diabetes are unable to achieve or maintain the American Diabetes Association's (ADA) recommended treatment goal of glycosylated hemoglobin A<sub>1C</sub> (A1C) levels below 7% (5). Inability to achieve adequate glycemic control early in the course of diabetes may stem in part from the typical conservative stepwise treatment approach exemplified as monotherapy initiated after failure with diet and exercise, followed by a combination of oral antiglycemic agents, and ultimately insulin therapy. The most obvious limitation of this approach is failure to swiftly address the dual pathophysiological defects, insulin resistance and progressive  $\beta$ -cell dysfunction, that are present at diagnosis in virtually all patients with type 2 diabetes (6). In the United Kingdom Prospective Diabetes Study (UKPDS), patients newly diagnosed with type 2 diabetes had evidence of an approximately 50% reduction in  $\beta$ -cell function as well as only 50% of normal insulin sensitivity (7). Because it is now appreciated that the use of a single antihyperglycemic agent corrects only one of these defects, initial monotherapy may be less than optimal for management of type 2 diabetes.

An alternative approach to achieving and maintaining glycemic control for patients with type 2 diabetes is the initial use of combination agents to simultaneously stimulate insulin secretion and reduce insulin resistance, as with a sul-

fonylurea and metformin (8). Sulfonylureas enhance insulin secretion, whereas metformin, among other actions, increases insulin sensitivity, resulting in reduced hepatic glucose output and increased glucose uptake in muscle (6). The current ADA practice guidelines recommend that combination therapy (e.g. biguanide and a sulfonylurea) is a secondary approach in patients for whom monotherapy fails (5). However, only one trial has been conducted to determine whether the simultaneous use of both an insulin sensitizer and an insulin secretagogue is a viable option for initial pharmacological therapy. In patients inadequately controlled by diet and exercise alone, initial therapy with glyburide/metformin tablets provided glycemic control superior to that of glyburide<sup>1</sup> or metformin monotherapy (9). Because entry into this placebo-controlled trial was necessarily restricted to patients with baseline A1C concentrations between 7–11%, patients with more severe hyperglycemia were excluded. Therefore, the present study was designed without placebo to examine the efficacy of initial therapy with glyburide/metformin tablets compared with traditional glyburide or metformin monotherapy in patients with more severe hyperglycemia.

## Materials and Methods

### Study design

The efficacy of glyburide/metformin tablets as initial therapy was assessed in patients with type 2 diabetes in a multicenter, randomized, three-arm, parallel group, double-blind trial. Patients with type 2 diabetes who were inadequately controlled (A1C, >7% and  $\leq$ 12%) with diet and exercise treatment alone were randomly assigned for 16 wk to

Abbreviations: ADA, American Diabetes Association; CI, confidence interval; FPG, fasting plasma glucose; GI, gastrointestinal; PPG, postprandial glucose; UKPDS, United Kingdom Prospective Diabetes Study.

<sup>1</sup>Non-U.S. equivalent is known as glibenclamide.

triple-dummy therapy with glyburide/metformin (1.25/250-mg tablets), metformin (500 mg) monotherapy, or glyburide (2.5 mg) monotherapy. Eligible patients were 20–78 yr old, had a diagnosis of type 2 diabetes for at least 3 months but no longer than 10 yr, had a body mass index of 23–40 kg/m<sup>2</sup>, gave informed consent, and were able to perform self-monitoring of blood glucose concentrations. Patients had not been previously treated with glucose-lowering agents or had been free from antihyperglycemic therapy for at least 8 wk before screening. Medications known to affect carbohydrate metabolism (e.g. corticosteroids, endocrine replacement therapy, oral contraceptives, diuretics, and lipid-lowering agents) were permitted concomitantly if patients were maintained on stable doses.

Patients with the following conditions were excluded from study participation: marked polyuria and polydipsia with greater than 10% weight loss; administration of antihyperglycemic agents within 8 wk before screening; a history of chronic insulin therapy, diabetic ketoacidosis, or hyperosmolar nonketotic coma; significant abnormal renal function defined by a serum creatinine concentration greater than or equal to 1.5 mg/dl (133 μmol/liter) for men and greater than or equal to 1.4 mg/dl (124 μmol/liter) for women; significant abnormal liver function defined as aspartate aminotransferase or alanine aminotransferase levels greater than or equal to twice the upper limit of normal or total serum bilirubin concentration greater than or equal to twice the upper limit of normal; alcohol and/or substance abuse within the year before screening; and cardiac or cerebral events within 6 months before screening.

### Treatment

During a 2-wk placebo lead-in phase, eligible patients were evaluated for compliance with triple-dummy placebo consumption, dietary guidelines established by the ADA, and self-monitoring of blood glucose recorded in log books. After obtaining written informed consent, the sites assigned randomization numbers in blocks according to sequence. The randomization was balanced within each site across the treatments in blocks of three. The allocation sequence was generated by the study sponsor before study initiation. All study personnel were blinded to treatment assignment throughout the duration of the study except in the event of an emergency. Upon initiation of double-blind, triple-dummy treatment, study medications were administered once daily (before the morning meal) during the first week and twice daily (before the morning and evening meals) during the second week. Adjustment of medication to therapeutic goal or maximum allowed daily dose was performed during wk 2, 4, 6, and 10 if the mean daily glucose level was greater than or equal to 126 mg/dl (7.0 mmol/liter) or during wk 10 if the A1C level was greater than or equal to 7%. Mean daily glucose values were calculated from the average of four fingerstick measurements (obtained before breakfast, before lunch, before dinner, and at bedtime) obtained 3–5 d before each clinic visit. The maximum allowable total daily doses were 2000 mg metformin, 10 mg glyburide, and 5/1000 mg glyburide/metformin. Downward adjustment occurred if fasting blood glucose was less than or equal to 50 mg/dl (2.8 mmol/liter) on one or more occasions, with or without symptoms of hypoglycemia.

Physical examination, laboratory analyses, including lipid panel, counseling on diet and glucose monitoring, fingerstick log measurements, and adverse events were performed or reviewed during clinic visits.

### Efficacy evaluation

The primary efficacy analysis included all randomly assigned patients with baseline data and at least one postbaseline measurement, whereas the safety analysis included all patients who received at least one dose of study medication. The primary efficacy variable was change in A1C level from baseline to wk 16 of the double-blind treatment period or the last prior visit.

### Statistical analysis

Comparisons of glyburide/metformin tablets with both monotherapies for superiority were performed using the Min test of Laska and Meisner within the framework of an analysis of covariance model with a term for treatment and the baseline value as the covariate. Statistical

significance for superiority of the combination therapy was to be declared if the larger of the 2 1-sided *P* values obtained by testing the combination therapy separately against the two monotherapies was less than 0.025, because the Min test was inherently 1-sided. With 150 patients/group, there was 90% statistical power to show superiority of glyburide/metformin tablets over both monotherapies if the mean reduction in A1C level was 0.37% greater than the mean reduction for each monotherapy. Ninety-five percent confidence intervals (CIs) for the differences between glyburide/metformin tablets and monotherapies also were constructed. Similar analyses were performed for the change from baseline to wk 16 or the last prior visit for the following variables: fasting plasma glucose (FPG), 2-h postprandial glucose [PPG; measured after a Boost Plus (formerly known as Sustacal) standard liquid meal challenge], fructosamine, and body weight. However, the Min test approach was not used. All tests for these secondary efficacy variables were 2-sided, with a significance level of 0.05.

## Results

A total of 513 patients were enrolled at 138 sites throughout the United States beginning May 1, 2000. The study was completed January 10, 2001. Of those enrolled, 486 patients were randomly assigned to treatment. Demographic characteristics were evenly distributed among the 3 treatment arms (Table 1). Four hundred and eighty-five patients were administered at least 1 dose of study medication (1 patient in the glyburide/metformin group was lost to follow-up), and 429 patients completed the double-blind study. Final mean doses for each treatment group after 16 wk of therapy were 3.7/735 mg glyburide/metformin, 1796 mg metformin, and 7.6 mg glyburide. The most common reasons for discontinuation were patient request (3.9%) and adverse events other than hypoglycemia (3.5%). Only 1 patient (0.6%) in the glyburide/metformin group discontinued therapy because of a lack of glycemic control compared with 2 patients (1.2%)

**TABLE 1.** Baseline demographic and diabetes characteristics and lipid profile

Characteristic	Glyburide/ metformin	Metformin	Glyburide
Randomized patients (no.)	171	164	151
Age [yr (±SD)]	55.6 (11.2)	54.7 (11.8)	55.3 (12.2)
Gender [no. (%)]			
Men	76 (44.4)	71 (43.3)	66 (43.7)
Women	95 (55.6)	93 (56.7)	85 (56.3)
Race [no. (%)]			
White	132 (77.2)	132 (80.5)	123 (81.5)
Black	18 (10.5)	11 (6.7)	11 (7.3)
Hispanic	15 (8.8)	15 (9.1)	12 (7.9)
Other	6 (3.5)	6 (3.7)	5 (3.3)
Body mass index (kg/m <sup>2</sup> )	31.4 (4.6)	31.4 (4.0)	31.1 (4.3)
Body weight (kg)	91.9 (17.4)	92.8 (15.6)	91.0 (16.0)
Duration of diabetes (yr)	3.0 (3.0)	2.6 (2.3)	3.0 (2.6)
A1C (%)	8.8 (1.5)	8.5 (1.4)	8.7 (1.4)
Fasting glucose (mg/dl)	191.2 (57.3)	189.5 (55.9)	188.8 (55.2)
Fasting insulin (μIU/ml)	15.9 (11.1)	16.3 (13.2)	16.7 (28.9)
Total cholesterol (mg/dl)	201.2 (4.0)	209.1 (4.0)	205.3 (3.8)
High density lipoprotein cholesterol (mg/dl)	41.3 (0.9)	42.3 (0.9)	41.6 (1.0)
Low density lipoprotein cholesterol (mg/dl)	118.3 (3.5)	122.7 (3.2)	122.2 (3.2)
Triglycerides (mg/dl)	248.4 (26.2)	256.8 (26.7)	236.3 (19.1)

Data are presented as the number (percentage) of patients for gender and race and as the mean (±SE) for lipids. All other data are presented as the mean (±SD). Conversion factors from milligrams per deciliter to millimoles per liter: plasma glucose, multiply by 0.05551; plasma cholesterol, multiply by 0.02586; plasma triglycerides, multiply by 0.01129.

in the metformin monotherapy group and 3 patients (2.0%) in the glyburide monotherapy group.

#### Glycemic control parameters

After 16 wk of therapy (Table 2), glyburide/metformin tablets provided a greater reduction in A1C level from baseline (−2.27%) compared with both metformin (−1.53%) and glyburide (−1.90%;  $P = 0.0003$ ; Fig. 1). Seventy-nine percent of patients in the glyburide/metformin treatment group had an A1C concentration less than 7% relative to 62% in the metformin monotherapy group and 68% in the glyburide monotherapy group (Fig. 2). A greater reduction from baseline also was observed when the glyburide/metformin tablets were used compared with either monotherapy when results were stratified by baseline A1C level (Fig. 3). After 16 wk of treatment, the

**TABLE 2.** Mean change from baseline to wk 16 or last visit in measures of glycemia and insulin

Parameter	Treatment group	Baseline	Change from baseline	<i>P</i> value (glyburide/metformin vs. monotherapy)
A1C (%)	Gly/Met	8.78	−2.27	<0.0001
	Met	8.42	−1.53	
	Gly	8.67	−1.90	
FPG (mg/dl)	Gly/Met	191.0	−62.4	<0.001
	Met	188.2	−43.8	
	Gly	189.7	−52.8	
2-h PPG (mg/dl)	Gly/Met	245.8	−82.5	0.016
	Met	232.2	−70.0	
	Gly	251.0	−62.6	
Fructosamine (mmol/liter)	Gly/Met	249.2	−49.0	<0.001
	Met	246.0	−33.8	
	Gly	248.1	−39.0	
Insulin ( $\mu$ IU/ml)	Gly/Met	15.0	1.3	0.027
	Met	16.1	−1.7	
	Gly	17.3	4.5	
2-h postprandial insulin ( $\mu$ IU/ml)	Gly/Met	45.7	20.3	<0.001
	Met	45.5	0.1	
	Gly	47.4	16.3	

Gly/Met, Glyburide/metformin tablets; Met, metformin monotherapy; Gly, glyburide monotherapy. To convert plasma glucose from milligrams per deciliter to millimoles per liter, multiply by 0.05551.

mean adjusted change from baseline in fructosamine values, which measure glycemic control over a 2- to 4-wk period, also was significantly ( $P < 0.001$ ) decreased by 49.0  $\mu$ mol/liter for the glyburide/metformin tablet group compared with either metformin (33.8  $\mu$ mol/liter) or glyburide (39.0  $\mu$ mol/liter).

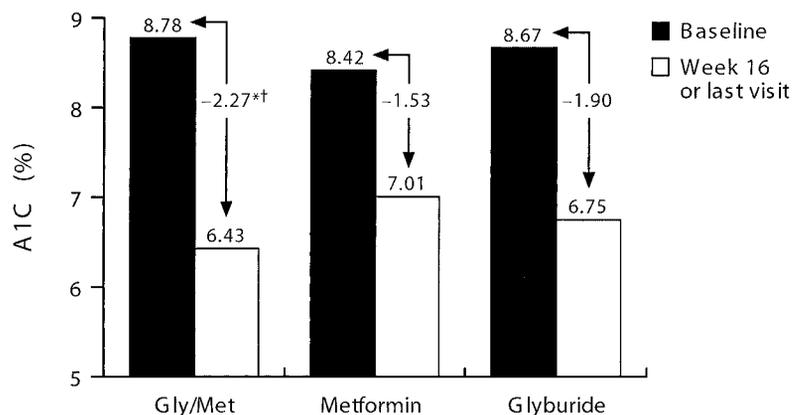
Therapy with glyburide/metformin tablets also was associated with significantly greater reductions in FPG and 2-h PPG values compared with either monotherapy (Fig. 4). From baseline, glyburide/metformin reduced FPG levels by −62.4 mg/dl (−3.5 mmol/liter), a greater reduction than either metformin [−43.8 mg/dl (−2.4 mmol/liter);  $P < 0.001$ ] or glyburide [−52.8 mg/dl (−2.9 mmol/liter);  $P = 0.007$ ] alone.

In addition, increases from baseline PPG levels measured 2 h after a standard liquid meal challenge were significantly less with the glyburide/metformin tablets [−82.5 mg/dl (−4.6 mmol/liter)] compared with metformin [−70.0 mg/dl (−3.9 mmol/liter);  $P = 0.016$ ] or glyburide [−62.6 mg/dl (−3.5 mmol/liter);  $P < 0.001$ ] monotherapy (Fig. 4). PPG excursions were calculated as the difference between 2-h PPG and FPG values. For glyburide/metformin tablets, metformin monotherapy, and glyburide monotherapy, mean 2-h PPG excursions at wk 16 were 33 mg/dl (1.8 mmol/liter), 28 mg/dl (1.6 mmol/liter), and 49 mg/dl (2.7 mmol/liter), respectively, and were greatly reduced relative to excursions measured at baseline [60 mg/dl (3.3 mmol/liter), 48 mg/dl (2.7 mmol/liter), and 63 mg/dl (3.5 mmol/liter), respectively;  $P < 0.05$  in each case].

#### Insulin concentrations

After 16 wk, the mean increase in fasting insulin concentrations for glyburide/metformin tablets (1.3  $\mu$ IU/ml) was significantly ( $P = 0.024$ ) less than the increase produced by glyburide (4.5  $\mu$ IU/ml). In contrast, metformin was associated with a significant reduction of −1.7  $\mu$ IU/ml ( $P = 0.027$ ). After 16 wk of therapy, the mean 2-h postprandial insulin response produced using a standardized glucose load was increased from baseline by 20.3  $\mu$ IU/ml for glyburide/metformin and 16.3  $\mu$ IU/ml for glyburide ( $P =$  NS for the difference between glyburide and glyburide/metformin). In

**FIG. 1.** Change in A1C concentrations to wk 16 or last visit.



\* $P = 0.0003$  compared with glyburide  
† $P < 0.0001$  compared with metformin

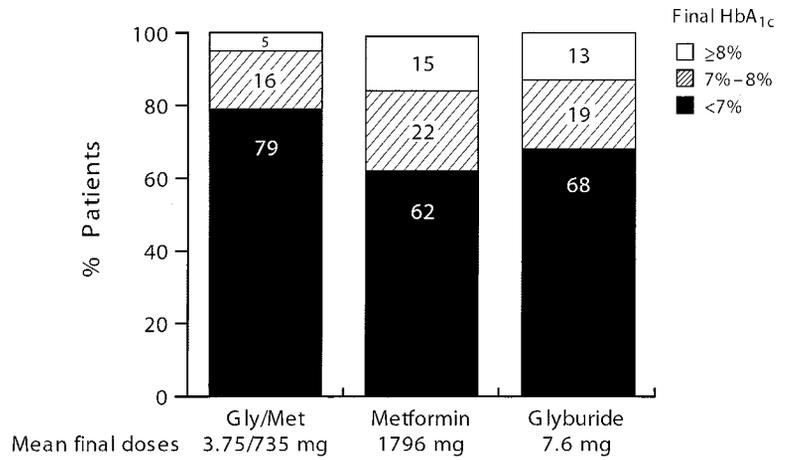


FIG. 2. Final A1C distribution to wk 16 or last visit.

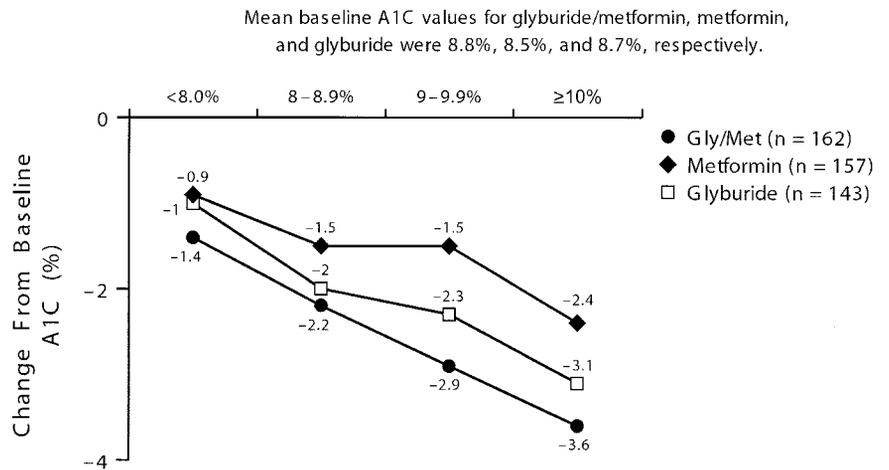


FIG. 3. Change in A1C levels to wk 16 or last visit stratified by baseline value.

contrast, the 2-h postprandial insulin response for metformin was unchanged from baseline ( $P < 0.001$  *vs.* glyburide/metformin).

**Body weight and lipid profile**

At wk 16, patients administered glyburide/metformin tablets had a mean increase in body weight of 1.6 kg compared with a mean increase of 2.0 kg ( $P = \text{NS}$ ) in patients administered glyburide monotherapy. Patients administered metformin therapy had a mean change of  $-1.1$  kg ( $P < 0.001$ ). At wk 16, glyburide/metformin tablets, metformin monotherapy, and glyburide monotherapy reduced triglyceride concentrations by  $-52.0$  mg/dl ( $-0.6$  mmol/liter;  $P < 0.05$ ),  $-39.6$  mg/dl ( $-0.4$  mmol/liter;  $P = \text{NS}$ ), and  $-15.1$  mg/dl ( $-0.2$  mmol/liter;  $P = \text{NS}$ ), respectively. Glyburide/metformin tablets, metformin monotherapy, and glyburide monotherapy produced changes in total cholesterol of  $-0.1$  mg/dl ( $-0.003$  mmol/liter;  $P = \text{NS}$ ),  $-10.5$  mg/dl ( $-0.3$  mmol/liter;  $P < 0.05$ ), and  $-1.5$  mg/dl ( $-0.04$  mmol/liter;  $P = \text{NS}$ ) from baseline, respectively. High density lipoprotein cholesterol was changed by  $0.8$  mg/dl ( $0.02$  mmol/liter),  $-0.4$  mg/dl ( $-0.01$  mmol/liter), and  $0.5$  mg/dl ( $0.01$  mmol/liter; all  $P = \text{NS}$ ); low density lipoprotein cholesterol was changed by  $4.5$  mg/dl ( $0.1$  mmol/liter;  $P < 0.05$ ),  $-5.7$  mg/dl ( $-0.1$  mmol/liter;  $P < 0.05$ ), and  $2.3$  mg/dl ( $0.1$

mmol/liter;  $P = \text{NS}$ ) for glyburide/metformin tablets, metformin monotherapy, and glyburide monotherapy, respectively.

**Safety**

Treatment emergent adverse events, regardless of causal relationship to the study medication, were reported in 79% of patients in the glyburide/metformin tablet group, 73% in the metformin monotherapy, and 76% in the glyburide monotherapy group (Table 3). All-cause serious adverse events occurred in 14 subjects, none of which were considered likely to be related to the study drugs, and no unexpected events were reported. Two deaths, both in the glyburide/metformin group, were not treatment related. The most common treatment emergent clinical adverse events were gastrointestinal (GI) events and hypoglycemia or symptoms of hypoglycemia. The most frequently reported GI symptoms were diarrhea, nausea/vomiting, and abdominal pain (18.9%, 11.6%, and 6.1%, respectively) for patients administered metformin. Among patients administered glyburide/metformin tablets, the frequency of these events (7.6%, 5.3%, and 4.1%, respectively) was significantly ( $P = 0.002$ ) lower than among those administered metformin and was similar to the occurrence among patients administered glyburide (6.0%, 7.3%, and 4.0%, respectively).

Symptoms suggestive of hypoglycemia were reported in

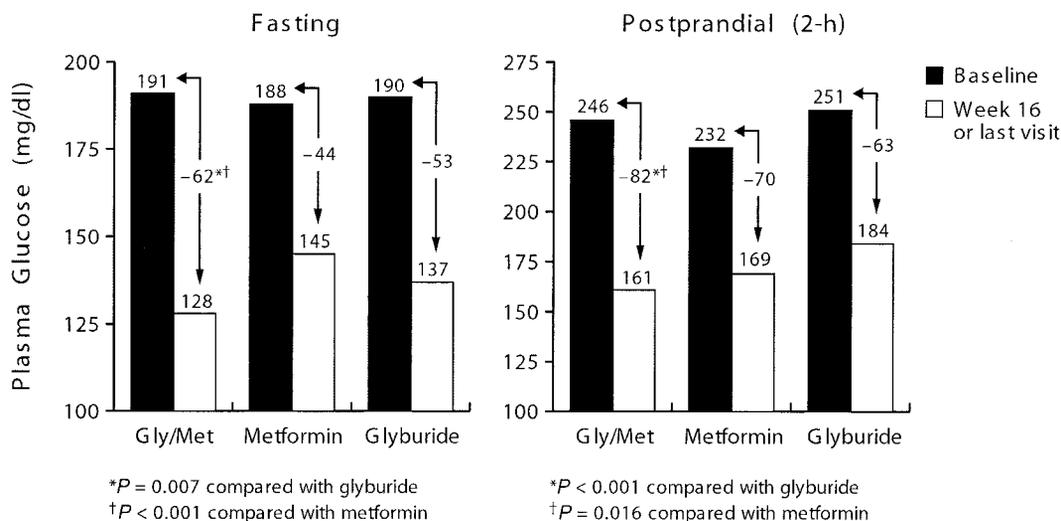


FIG. 4. Change in fasting and 2-h postprandial plasma glucose parameters to wk 16 or last visit. To convert plasma glucose values from milligrams per deciliter to millimoles per liter, multiply by 0.05551.

**TABLE 3.** Most common treatment-emergent clinical adverse events ( $\geq 5\%$  frequency) during and up to 14 d after double-blind therapy, except hypoglycemia or symptoms of hypoglycemia

Adverse event	No. (%) of patients		
	Glyburide/ metformin	Metformin	Glyburide
Diarrhea	13 (7.6)	30 (18.3)	8 (5.3)
Upper respiratory infection	15 (8.8)	18 (11.0)	15 (9.9)
Nausea/vomiting	8 (4.7)	17 (10.4)	10 (6.6)
Musculoskeletal pain	11 (6.5)	16 (9.8)	13 (8.6)
Headache	16 (9.4)	8 (4.9)	8 (5.3)
Abdominal pain	7 (4.1)	10 (6.1)	6 (4.0)
Total patients with at least 1 event <sup>a</sup>	134 (78.8)	120 (73.2)	114 (75.5)

<sup>a</sup> For each treatment regimen, the total of patients experiencing at least one event is less than the sum of the patients counted under each type of event. This is because some patients experienced more than one event (of different types) and are counted under each type of event that they experienced.

17.7% patients administered metformin, 39.1% of those administered glyburide, and 57.6% of those administered glyburide/metformin tablets. However, fingerstick blood glucose concentrations were less than or equal to 50 mg/dl (2.8 mmol/liter) in only 0.6%, 10.6%, and 11.2% of these patients administered metformin, glyburide, or glyburide/metformin tablets, respectively. No patient in the trial required medical assistance to manage hypoglycemia.

### Discussion

This study demonstrates that initial treatment with glyburide/metformin tablets provides superior glycemic control at lower doses than individual monotherapies in patients with type 2 diabetes in whom diet and exercise have failed. The improvements in all measures of glycemic control provided by glyburide/metformin tablets, including A1C, fructosamine, FPG, and PPG concentrations, were superior to either monotherapy. The findings of this study, which randomized patients with higher baseline A1C concentrations due to the elimination of a placebo control group, demon-

strate the superiority of glyburide/metformin tablets in a diverse and clinically representative population of patients with type 2 diabetes. Therefore, the present results extend the findings of the previously mentioned placebo-controlled trial in which baseline A1C concentrations were lower and reductions in A1C and postprandial glucose concentrations produced by initial therapy with glyburide/metformin tablets were significantly greater than those provided by glyburide or metformin monotherapy (9). The present study reveals improved efficacy at all baseline A1C concentrations in a more diverse patient population that more closely approximates real-world clinical practice.

Therapy with glyburide/metformin tablets was associated with a mean A1C reduction of  $-2.27\%$  from baseline, a significant improvement compared with both metformin and glyburide alone ( $P = 0.0003$ ). Moreover, a greater reduction from baseline was achieved with glyburide/metformin tablets *vs.* glyburide or metformin alone regardless of baseline A1C values, and a greater percentage of patients receiving glyburide/metformin therapy were able to achieve the ADA treatment goal of A1C concentration less than 7%. Treatment outcomes stratified by baseline A1C showed greater treatment benefits with higher baseline values. This was achieved at nearly half the dose of each monotherapy and with no more biochemically documented hypoglycemic episodes [fingerstick glucose,  $\leq 50$  mg/dl (2.8 mmol/liter)] compared with those documented in the glyburide monotherapy group. The mean final metformin dose in the glyburide/metformin group was 735 mg daily, which was associated with significantly fewer GI adverse events *vs.* the metformin monotherapy group with a mean final dose of 1796 mg daily.

The benefits of improved glycemic control in type 2 diabetes have been demonstrated in the UKPDS. In an analysis of all participants in the UKPDS, the risk for microvascular or microvascular complications in patients with type 2 diabetes was confirmed to be strongly associated with total glycemic burden (4). Each 1% reduction in mean A1C concentration was associated with reductions in risk of 21% for

any end point related to diabetes (95% CI, 17–24%;  $P < 0.0001$ ), 21% for deaths related to diabetes (95% CI, 15–27%;  $P < 0.0001$ ), 14% for myocardial infarction (95% CI, 8–21%;  $P < 0.0001$ ), and 37% for microvascular complications (95% CI, 33–41%;  $P < 0.0001$ ). It was concluded that any reduction in A1C concentration is likely to reduce the risk for complications associated with type 2 diabetes. Therefore, treatment that can offer patients enhanced glycemic control initially by preventing excessive glucose exposure is unquestionably and fundamentally imperative to reduce the risks for long-term complications.

In addition to reducing A1C values to a greater extent than either monotherapy, glyburide/metformin tablets produced greater reductions in FPG, mean 2-h PPG levels, and PPG excursions. Because overall glycemic control is dependent on both fasting and postprandial plasma glucose concentrations, the use of a therapy that treats both the fasting and postprandial components of hyperglycemia is advantageous. The average final doses of the glyburide and metformin components required to obtain this degree of efficacy were less than half the component doses required in the monotherapy arms. This synergistic effect may be partially explained by an appropriate increase in postprandial insulin response in tandem with enhanced tissue sensitivity to insulin. The glyburide/metformin tablets were formulated with a spectrum of glyburide particle sizes (10), leading to more rapid dissolution of the smaller particles and an earlier increase in plasma glyburide levels compared with conventional Micronase (glyburide tablets, USP; Pharmacia & Upjohn, Kalamazoo, MI) used with metformin. A 2-fold increase in glyburide levels with glyburide/metformin tablets within the first 3 h of treatment may contribute to the larger postprandial insulin response and better control of postprandial glucose concentrations (11).

The use of combination glyburide/metformin tablets in the current trial was tolerable, with overall rates of adverse reactions similar to those reported with each monotherapy component. GI adverse reactions were significantly reduced among those receiving the glyburide/metformin combination therapy compared with metformin monotherapy ( $P = 0.002$ ). This finding was also reported in an earlier trial in which GI adverse reactions were significantly lower in glyburide/metformin-treated patients (32%) compared with metformin monotherapy (43%;  $P = 0.037$ ) (9). The likely reason for the fewer GI adverse reactions after glyburide/metformin use in the current trial was the lower mean metformin dose required at wk 16 to maintain glycemic control (735 mg) compared with metformin monotherapy (1796 mg).

The design of this study required investigators to proactively question patients about the appearance of symptoms reminiscent of hypoglycemia, such as flushing, sweating, and dizziness. As a result, the reported incidence of symptoms of hypoglycemia was high in all treatment groups. For example, it is generally accepted that metformin is not associated with clinically significant hypoglycemia (12), although 17.7% of patients reported symptoms of hypoglycemia in the present study. It is well accepted that rapid falls in blood glucose can induce symptoms of hypoglycemia even when blood glucose does not actually reach the hypoglycemic range. The higher incidence of reported hypogly-

cemia in the glyburide/metformin group compared with the glyburide group is therefore consistent with the greater blood glucose-lowering effects observed. In contrast, the incidence of hypoglycemia confirmed by fingerstick glucose of 50 mg/dl or less (2.8 mmol/liter) was low and comparable in the glyburide monotherapy and glyburide/metformin groups (11% in each). Furthermore, this incidence of hypoglycemia was well within the range of reported incidences of hypoglycemia in sulfonylurea-naïve patients receiving glyburide/metformin (18% of patients) (8) or other combinations of metformin with an insulin secretagogue, such as glimepiride (22%) (13) or repaglinide (33%) (14).

Although the current study did not examine long-term safety, concern has been raised based on the overweight UKPDS study in which patients receiving sulfonylurea monotherapy had a lower cardiovascular death rate than those given combination therapy with sulfonylurea and metformin (2). It is important to point out that further analysis of this UKPDS study did not support increased mortality for patients receiving sulfonylurea and metformin therapy (2, 15). Specifically, it was concluded that the apparent increase in mortality in the combination group was due to an unexpectedly low mortality in the sulfonylurea alone group in the substudy (15). Thus, analysis of the data from the UKPDS study as a whole demonstrated that there was no increased risk after the coadministration of sulfonylurea and metformin.

Although the UKPDS is the only prospective study of clinical outcomes to date in patients receiving sulfonylurea/metformin combination therapy, retrospective studies have suggested the possibility of adverse outcomes in patients receiving a combination of a sulfonylurea with metformin compared with one or other agent given alone (16, 17). In clinical practice, combination therapy is most often prescribed after the failure of oral antidiabetic monotherapy to control blood glucose effectively. Type 2 diabetes may have therefore been more advanced in patients receiving the combination, so that increased mortality in such patients would not be surprising. A further population-based retrospective analysis avoided this confounding factor by including only patients receiving a sulfonylurea, metformin, or the two agents in combination, as initial pharmacological therapy for type 2 diabetes (18). In this analysis, patients in the sulfonylurea/metformin group had a significantly lower risk of all-cause or cardiovascular mortality compared with patients receiving sulfonylurea alone.

Persistence with medications is a key element in effective management of any chronic disease, and this is particularly important in diabetes. A combination product should enhance administration convenience for the patient and may offer persistence advantages. Research on combination products in hypertension (19) and in diabetes (20, 21) has shown that patients who receive a single treatment are more adherent to therapy than patients who take more complex regimens. By analogy, the glyburide/metformin tablet could be expected to enhance patient compliance and persistence (22) and, by extension, glycemic control and clinical outcomes.

In summary, glyburide/metformin tablets provide superior efficacy as initial therapy in patients with varying de-

grees of hyperglycemia who have failed diet and exercise. Therapy with glyburide/metformin tablets offers patients the benefit of achieving more intensive glycemic control in a shorter time, with fewer GI adverse events and no additional episodes of hypoglycemia. Therefore, glyburide/metformin tablets are a safe and effective choice as initial pharmacotherapy for patients with type 2 diabetes.

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