

# Beginning Insulin Treatment of Obese Patients With Evening 70/30 Insulin Plus Glimepiride Versus Insulin Alone

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**OBJECTIVE** — This study tested a simple algorithm for beginning insulin for obese patients with type 2 diabetes after sulfonylurea failure, comparing supertime 70/30 insulin plus continued glimepiride with insulin alone.

**RESEARCH DESIGN AND METHODS** — This was a multicenter ambulatory randomized double-masked parallel comparison. There were 208 subjects with secondary failure to sulfonylureas who took glimepiride titrated to 8 mg b.i.d. for 8 weeks; 145 subjects with fasting plasma glucose (FPG) 180–300 mg/dl (10–16.7 mmol/l) on this treatment were randomized to placebo plus insulin (PI) or glimepiride plus insulin (GI) for 24 weeks. A dosage of 70/30 insulin before supper was titrated, seeking fasting capillary blood glucose (FBG) 120 mg/dl (6.7 mmol/l), equivalent to FPG 140 mg/dl (7.8 mmol/l). Outcome measures included FPG, HbA<sub>1c</sub>, insulin dosage, weight, serum insulin and lipids, and adverse events.

**RESULTS** — FPG and HbA<sub>1c</sub> were equivalent at baseline: 261 vs. 250 mg/dl (14.5 vs. 13.9 mmol/l), and 9.9 vs. 9.7%. At 24 weeks, the FPG target was achieved in both groups (136 vs. 138 mg/dl, 7.6 vs. 7.6 mmol/l), and HbA<sub>1c</sub> values were equal (7.7 vs. 7.6%). However, with GI, control improved faster and fewer subjects dropped out (3 vs. 15%,  $P < 0.01$ ), and less insulin was needed (49 vs. 78 U/d,  $P < 0.001$ ). The outcomes were alike in other respects. No subject had severe hypoglycemia.

**CONCLUSIONS** — Injection of 70/30 insulin before supper safely restored glycemic control of type 2 diabetes not controlled by glimepiride alone. Control was restored more rapidly and with less injected insulin when glimepiride was continued.

Sulfonylurea treatment of type 2 diabetes undergoes secondary failure at a rate between 5 and 20% yearly (1,2). Consequently, initially effective treatment with a sulfonylurea commonly fails within 5 years. Early results of the U.K. Prospective Study of treatments of type 2 diabetes (3) show that secondary failure is not limited to sulfonylureas, but occurs at similar rates with diet and metformin as well. Thus, type 2 diabetes is progressive, combinations of treatments are routinely

needed, and insulin often becomes necessary when oral agents fail.

Unfortunately, beginning insulin may be considered problematic for obese patients with type 2 diabetes, and marked hyperglycemia may be permitted before insulin is started. For example, a recent report of clinical experience by generalist physicians in a major health system (4) showed that insulin was started at HbA<sub>1c</sub> 9.3%, with improvement only to 8.4% 1 year later, well above the 8% level considered acceptable. These

findings were interpreted as showing that insulin is relatively ineffective in clinical practice. Recent findings show that a new approach may give better results. Instead of stopping oral agents and starting two injections of insulin, as is often recommended, sulfonylureas and other oral agents may be continued while insulin is started as a single injection of NPH at bedtime or 70/30 before supper. Several small studies have shown that evening-insulin combined therapy restores glycemic control at the time of sulfonylurea failure more effectively than a single injection of insulin alone (5–7). A multicenter trial showed that evening-insulin combined therapy was as effective as multiple insulin injections alone and had less tendency to cause weight gain and hyperinsulinemia (8). Other studies confirm that less weight gain occurs with evening-insulin combined therapy than with multiple injections (9,10).

Up to now, however, no large controlled trial has studied the safety and efficacy of beginning insulin therapy in this way under conditions resembling those of clinical practice. That is, this approach has not been tested for obese patients seeking a level of control consistent with current recommendations but without frequent office visits and intensive glucose monitoring. We report here a multicenter trial simulating these conditions, using a single injection of insulin with or without continued use of the new sulfonylurea glimepiride (Amaryl; Hoechst Marion Roussel, Somerville, NJ and Kansas City, MO) (11–13). The trial was not intended to show the maximal glucose-lowering power of this method, but instead how consistently and safely a common clinical target can be reached using a simple algorithm.

The American Diabetes Association recommends that action be taken to improve control when fasting capillary blood glucose (FBG) is  $>140$  mg/dl (7.8 mmol/l) or HbA<sub>1c</sub> is  $>8\%$  (14). The recommended target range for FBG is 80–120 mg/dl (4.4–6.7 mmol/l) (14). This study compared the effectiveness of placebo plus insulin (PI) with that of glimepiride plus insulin (GI) in restoring FBG to 120 mg/dl, the upper end

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**Abbreviations:** FBG, fasting capillary blood glucose; FPG, fasting blood glucose; GI, glimepiride plus insulin; PI, placebo plus insulin.

of this target range. This level corresponds roughly to a fasting plasma glucose (FPG) of 140 mg/dl, as measured in a laboratory. Insulin was given as a single injection of 70/30 insulin before the evening meal. The rationale for using this kind and timing of insulin was that obese patients using large doses of insulin are believed to absorb insulin more slowly than slender, active individuals and to eat a large fraction of their daily calories at dinnertime. Thus, the NPH insulin component should peak close to breakfast time, and the regular insulin component should help control glycemia after a large evening meal. The safety and effectiveness of this method was shown in a previous study of obese patients starting insulin (6).

## RESEARCH DESIGN AND METHODS

### Subjects

The subjects were patients with type 2 diabetes who had successfully used a sulfonylurea for at least 6 months but were not subsequently well controlled with full dosage. They were between 45 and 70 years old and weighed between 130 and 170% of desirable weight at entry. Exclusion criteria included pregnancy or nursing; duration of diabetes >15 years; history of ketoacidosis, autoimmune disease, or major systemic illness other than diabetes; allergy or intolerance to sulfonylureas; use of glucocorticoid agents, phenytoin, nicotinic acid, sympathomimetics, phenothiazines, or isoniazid; serum creatinine or serum alanine aminotransferase >1.5 times the upper limit of normal; and fasting serum C-peptide <0.4 pmol/ml. Women were postmenopausal, infertile because of hysterectomy or other procedure, or used an adequate contraceptive method. All subjects had to perform accurate self-glucose monitoring and to grant informed consent.

### Open-label period

Eligible subjects discontinued their previous hypoglycemic therapy and were given glimepiride alone at doses titrated up to 8 mg twice daily for 8 weeks. The initial dosage was 8 mg before breakfast. FPG was tested at weekly intervals, and if the value was >150 mg/dl (8.3 mmol/l), the dosage was increased incrementally to 12 mg once daily, 16 mg once daily, and finally to 8 mg before breakfast and before supper after 3 weeks of treatment. If the FPG was <150 mg/dl on two consecutive visits, the patient was dropped from the study. Subjects were

also ineligible to continue if, after 2 weeks of treatment with 8 mg glimepiride twice daily, their FPG was  $\leq$ 180 mg/dl (10 mmol/l) or >300 mg/dl (16.7 mmol/l). Those continuing treatment took 8 mg twice daily to the end of the 8-week open-label period.

### Randomized treatment period

Subjects who completed the open-label phase were randomized to treatment with either GI or PI. Those in the GI group continued with glimepiride 8 mg twice daily, before breakfast and supper, while those in the PI group took placebo on the same schedule in a double-masked manner. Medication adherence, judged by pill counting, was better than 80%. All subjects started 70/30 (70% NPH insulin/30% regular insulin) human insulin injected 30 min before supper, which was usually close to 1800. The initial dosage was 10 U/day for the first 2 weeks. After that, the dosage was titrated upward according to FBG measurements taken by the subjects using a One-Touch II glucose meter (Lifescan, Milpitas, CA). The subjects were asked to measure capillary blood glucose before breakfast and supper daily, and they were in weekly phone contact with study personnel to agree on changes of insulin. Insulin dosage was increased by 10 U weekly until FBG was  $\leq$ 140 mg/dl (7.8 mmol/l) for 2 consecutive days, then 5 U weekly until FBG was  $\leq$ 120 mg/dl (6.7 mmol/l) for 2 consecutive days. Once the FBG was consistently 100 mg/dl (5.5 mmol/l) to 120 mg/dl, a constant insulin dosage was maintained. Small decreases of insulin were permitted to curtail symptoms suggesting hypoglycemia.

### Measures of outcome

Subjects visited the clinic weekly during the open-label phase, at baseline and 2 and 4 weeks into the randomized treatment phase, then every 4 weeks thereafter to the end of the 24-week treatment period. Insulin dosage, weight, vital signs, and FPG measurements were obtained at all visits. HbA<sub>1c</sub> was measured at all visits during the randomized treatment period. Samples for fasting plasma insulin, serum C-peptide, and lipoproteins were taken at randomization and at the end of the study. Subjects were discontinued from the study if they had FPG >300 mg/dl (16.7 mmol/l) on two consecutive visits after randomization.

### Laboratory analytical methods

Clinical analyses, including glucose and lipoproteins, were performed by Smith-

Kline Beecham, Van Nuys, CA. Because LDL cholesterol was estimated by Friedewald's formula (15), patients with very high triglyceride values were not included in the LDL analyses. Insulin and C-peptide were measured by immunoassay and HbA<sub>1c</sub> (normal range 4–6%) by high pressure liquid chromatography, all at the Diagnostic Diabetes Laboratory of the University of Missouri-Columbia.

### Statistical analysis

The main outcome measures were the FPG and HbA<sub>1c</sub> values during and at completion of the randomized treatment period, the declines of these measures from baseline values, and the dosage of insulin during maintenance and at the end point. An analysis of variance model was used to evaluate change of HbA<sub>1c</sub> from baseline to end point and change of FPG from baseline to week 2. The Mantel-Haenszel test and Wilcoxon's signed-rank test were used to examine between-treatment difference and change from baseline, respectively. The proportional hazards model was used to evaluate insulin dosage. All subjects with baseline and postbaseline data were included in each analysis except the proportional hazards model analysis, for which four subjects were excluded because of lack of complete data. Throughout the text, the data are presented as means  $\pm$  SD.

### Safety evaluations

Weight, vital signs, and history of adverse events were monitored at each visit. The subjects were encouraged to report symptoms they thought might be due to hypoglycemia, even if unverified by tests. By the subjects' report and the investigators' judgment, these symptoms were divided into mild, moderate, and severe. At selected visits, clinical chemistry and lipid profiles, complete blood counts, and urinalyses were performed. All patients had an electrocardiographic evaluation at baseline and at study end point.

## RESULTS

### Open-label run-in period

There were 208 subjects meeting the initial criteria who entered the open-label treatment period. Of these, 32 were disqualified for having glucose values above or below the range acceptable for the study. In addition, 31 were discontinued for administrative reasons, such as incomplete screening data, unreliability in adhering to the proto-

**Table 1—Baseline characteristics of all randomized subjects**

	PI	GI
<i>n</i>	73	72
Sex (F/M)	33/40	27/45
Age (years)	58 ± 8	58 ± 8
Ethnic background		
Caucasian	58	57
Latino, African-American, or Native American	15	15
BMI (kg/m <sup>2</sup> )	33.7 ± 5.4	32.2 ± 4.4
Duration of diabetes (years)	7 ± 4	7 ± 4
HbA <sub>1c</sub> (%)	9.9	9.7
FPG		
mg/dl	261	250
mmol/l	14.5	13.9

Data are *n* or means ± SD.

col, or adverse events. Of these 31, 8 were discontinued for adverse events. Five adverse events were judged possibly or probably related to glimepiride: two cases of rash and one each of diarrhea, thrombocytopenia, and urticaria.

**Randomized treatment period**

**Baseline clinical characteristics.** After the run-in period, 145 subjects remained eligible and were randomized, 73 to PI and 72 to GI. As shown in Table 1, the groups were alike at baseline in sex, age, ethnic distribution, BMI, duration of diabetes, and glycemic control.

**Adverse events and subjects not completing the protocol.** The proportion of subjects reporting an adverse event of any kind was the same in the two treatment groups: 90% of the PI group and 92% of the GI group. The most common adverse event for both groups was occurrence of symptoms compatible with hypoglycemia though not confirmed by blood test. Such symptoms were reported by 37% of the PI and 51% of the GI subjects (*P* < 0.05). Symptoms compatible with moderate hypoglycemia were reported by 15% of the PI and 11% of the GI subjects; these were not statistically different. All episodes were transitory, and they did not occur more frequently in any particular week during the treatment period. They occurred more often in the evening than at other times of the day. No subject experienced hypoglycemia that required assistance, and none of the events was judged by the investigators

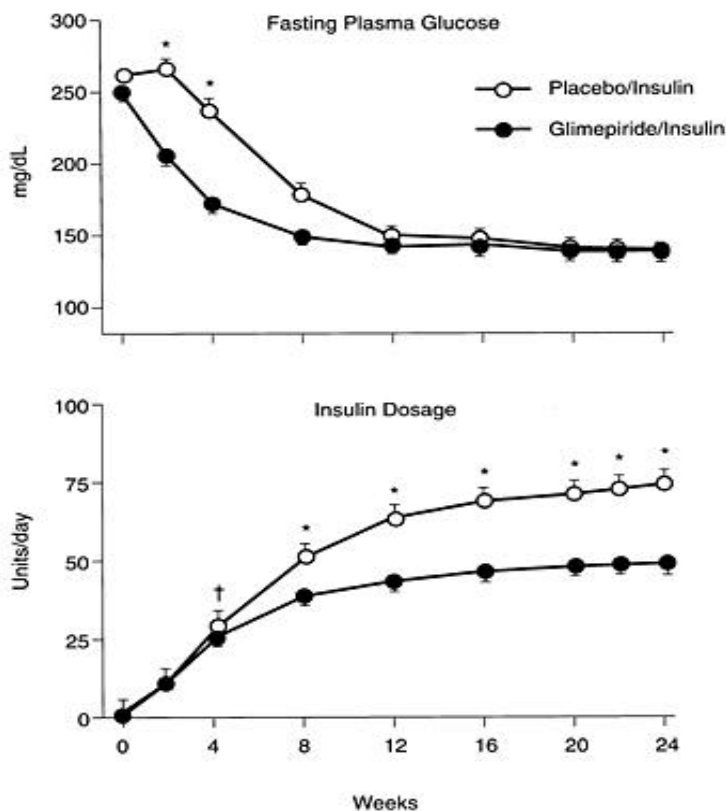
to be severe. No subject was discontinued from the study for hypoglycemia.

Serious adverse events were experienced by three subjects in the PI group (myocardial infarction, gastritis, and vitrectomy) and five in the GI group (cerebrovascular accident, cardiac surgery, abscess, thrombophlebitis, and carcinoma). None of these was considered related to the treatments. No patient died during the trial or a 14-day follow-up period. There were no noteworthy changes of clinical laboratory values, electrocardiographic findings, or physical examinations other than those previously stated.

Overall, 13 subjects did not complete the entire randomized treatment period. Significantly more were discontinued from the PI group (11 of 73, 15%) than from the GI group (2 of 72, 3%) (*P* < 0.01). Neither of the noncompleters from the GI group did so because of hyperglycemia or adverse events. Of the 11 subjects discontinued from the PI group, 3 had FPG persistently >300 mg/dl (16.7 mmol/l). Three others had adverse events (dizziness, worsening

retinopathy, and symptomatic neuropathy) that were potentially related to glycemic control. Two other subjects were discontinued for perceived ineffectiveness of the treatment.

**Glycemic responses to treatment.** The glycemic responses of all subjects starting insulin treatment are shown in Fig. 1. The mean FPG at baseline after 8 weeks of glimepiride monotherapy was equivalent in the two groups: (mean ± SD) 261 ± 42 mg/dl (14.5 ± 2.3 mmol/l) for PI vs. 250 ± 45 mg/dl (13.9 ± 2.5 mmol/l) for GI. Mean HbA<sub>1c</sub> values were also equivalent at baseline: 9.9 ± 1.3% for PI vs. 9.7 ± 1.3% for GI. Most subjects reported reaching the self-measured FBG target, 120 mg/dl (6.7 mmol/l), although the percentage was higher in the GI subjects (81% of PI and 95% of GI). The mean laboratory-measured FPG for both groups reached the predicted level, ~140 mg/dl (7.8 mmol/l), after 12 weeks of treatment and remained there to the end of the study. For the subjects who completed the entire treatment period, the mean FPG at 24 weeks was 136



**Figure 1—Mean FPG and daily insulin dosage for all subjects in the two groups treated with insulin. There were 73 subjects randomized to PI and 72 to GI, of whom 62 and 70 subjects, respectively, completed the study\**P* < 0.001, †*P* < 0.05 for significant between-group differences. Mean ± SEM or means – SEM are shown.**

$\pm 39$  mg/dl ( $7.6 \pm 2.2$  mmol/l) for PI and  $138 \pm 33$  mg/dl ( $7.6 \pm 1.8$  mmol/l) for GI. HbA<sub>1c</sub> values for the two groups were similar at 24 weeks:  $7.7 \pm 1.0\%$  for PI and  $7.6 \pm 0.8\%$  for GI. The declines of HbA<sub>1c</sub> from baseline values were also equivalent for the two treatments,  $2.1 \pm 1.0\%$  for PI and  $2.2 \pm 1.0\%$  for GI.

However, FPG did not decrease at the same rate in the two treatment groups (Fig. 1). At 2 weeks, the FPG for PI was  $266 \pm 60$  mg/dl ( $14.8 \pm 3.3$  mmol/l),  $236 \pm 68$  mg/dl ( $13.1 \pm 3.8$  mmol/l) at 4 weeks, and  $178 \pm 57$  mg/dl ( $9.9 \pm 3.2$  mmol/l) at eight weeks. In contrast, the FPG for GI declined immediately to  $205 \pm 46$  mg/dl ( $11.4 \pm 2.6$  mmol/l) at 2 weeks, to  $172 \pm 46$  mg/dl ( $9.6 \pm 2.6$  mmol/l) at 4 weeks, and  $148 \pm 36$  mg/dl ( $8.2 \pm 2.0$  mmol/l) at 8 weeks. The between-treatment differences were statistically significant at 2 and 4 weeks. The glucose responses were most divergent ( $P < 0.001$ ) at 2 weeks, when FPG increased slightly in the PI group but decreased by 46 mg/dl ( $2.5$  mmol/l) in the GI group. The 12-week mean HbA<sub>1c</sub> values reflected the difference in the rate of improvement of glycemic control: 8.9% for PI compared with 7.9% for GI ( $P < 0.001$ ).

**Insulin requirement.** The average weekly insulin dosages for all subjects in the two treatment groups are shown in Fig. 1. As FBG and FPG approached the target range after 12 weeks, the insulin dosage curves for both groups also stabilized. At all times after 2 weeks, the mean dosage for the PI group was significantly greater than that for the GI group. The values at end point (24 weeks or at the time of discontinuation) were 78 U/day for PI and 49 U/day for GI ( $P < 0.001$ ). Of 73 PI subjects, 9 (14%) needed  $>100$  U/day, compared with 4 of 72 GI subjects (6%).

**Clinical and metabolic effects for subjects who completed the study.** Figure 1 includes data for all subjects starting insulin, whether they completed the protocol or not. To further examine the metabolic and clinical effects of the two regimens, several measurements were compared from baseline to 24 weeks for the 62 of 73 PI subjects and 70 of 72 GI subjects who completed the entire treatment period, excluding the baseline values of those who dropped out (Table 2).

At 24 weeks, when glycemic control was stable and equivalent in the two groups, the mean insulin dosage was 73 U/day for PI subjects and 49 U/day for GI subjects. Blood pressure was not altered by either

**Table 2—Comparison of the clinical and metabolic effects of treatment for the subjects completing the study**

	PI		GI	
	Baseline	24 weeks	Baseline	24 weeks
<i>n</i>	62		70	
HbA <sub>1c</sub> (%)	$9.8 \pm 1.3$	$7.7 \pm 1.0$	$9.7 \pm 1.3$	$7.6 \pm 0.8$
Weight (kg)	$99.2 \pm 20.8$	$103.2 \pm 20.3$	$93.9 \pm 15.9$	$98.2 \pm 16.5$
Blood pressure (mmHg)				
Systolic	$137 \pm 17$	$135 \pm 17$	$132 \pm 16$	$134 \pm 16$
Diastolic	$81 \pm 9$	$80 \pm 8$	$80 \pm 8$	$80 \pm 9$
Fasting serum insulin ( $\mu$ U/ml)	$20.1 \pm 19.0$	$28.7 \pm 21.5$	$16.8 \pm 15.8$	$27.4 \pm 22.0$
Fasting serum C-peptide (pmol/ml)	$1.3 \pm 0.6$	$0.6 \pm 0.4$	$1.2 \pm 0.6$	$0.8 \pm 0.3^*$
Fasting serum lipids (mg/dl)				
Total cholesterol	$220 \pm 44$	$213 \pm 35$	$228 \pm 48$	$217 \pm 43$
LDL cholesterol	$124 \pm 37$	$126 \pm 32$	$132 \pm 36$	$130 \pm 31$
HDL cholesterol	$45 \pm 11$	$50 \pm 12$	$47 \pm 9$	$48 \pm 10^\dagger$
Triglycerides	$276 \pm 182$	$182 \pm 93$	$280 \pm 295$	$206 \pm 175$

Data are means  $\pm$  SD. \* $P < 0.001$ ,  $^\dagger P < 0.05$  for between-group differences in change from baseline.

treatment. The groups showed similar gains of weight at 24 weeks, an average of 4.0 kg (8.9 lb) for PI subjects and 4.3 kg (9.4 lb) for GI subjects. Fasting insulin increased significantly and equivalently with both treatments (from 20.1 to 28.7  $\mu$ U/ml with PI,  $P < 0.001$  and from 16.8 to 27.4  $\mu$ U/ml with GI,  $P < 0.001$ ). Fasting C-peptide declined from baseline after insulin treatment in both groups, but significantly more ( $P < 0.001$ ) with PI than GI. Triglyceride concentrations were significantly and equivalently lower at 24 weeks with both PI and GI. HDL cholesterol concentrations increased with both, but the change for PI was slightly greater ( $P < 0.05$ ) than that for GI. LDL cholesterol was not significantly changed by either treatment.

**CONCLUSIONS**— The effectiveness of combining an evening injection of insulin with a sulfonylurea when sulfonylurea monotherapy fails has been documented previously. A study of mildly obese subjects found that adding a fixed dose of 20 U NPH insulin at bedtime while continuing 20 mg glipizide twice daily reduced FPG to 144 mg/dl (8 mmol/l) and HbA<sub>1c</sub> to 7.6% (7). This HbA<sub>1c</sub> value was 2.1% lower than that obtained with the same dose of insulin plus placebo. In the same study, increasing the insulin dosage as much as possible without hypoglycemia reduced FPG to 113 mg/dl (6.3 mmol/l) and HbA<sub>1c</sub> to 7.1%, 1.2% lower than with insulin alone (7). Another study (6) of more obese NIDDM subjects used 70/30 insulin before supper with

dosage increased to tolerance, along with 10 mg of glyburide daily. This combination reduced FPG to 106 mg/dl (5.9 mmol/l), while subjects treated with 70/30 insulin plus placebo had FPG 135 mg/dl (7.5 mmol/l). Thus, both a low fixed dose and the highest tolerated dose of evening insulin reduced FPG and HbA<sub>1c</sub> more effectively when a sulfonylurea was continued.

Rather than repeating these previous studies, the present study examined whether this way of starting insulin can be applied to the situation in which most patients with type 2 diabetes actually are treated. Instead of using a fixed dose of insulin or titrating the dose to the point of hypoglycemia, physicians more often start with a low dose and increase it gradually, seeking moderate control. In this study, insulin was started at 10 U/day and increased 5 or 10 U weekly based on the subjects' daily FBG tests until the target value of 120 mg/dl was reached. The study's design was a balance of simplicity, simulating conditions of clinical practice, and allowing enough glucose testing (twice daily) and contact with study personnel (weekly phone contact and monthly visits) to permit evaluation of both the adverse effects and the effectiveness of these tactics. The subjects selected were likely to have relatively difficult-to-control diabetes, being quite obese and with very high FPGs on glimepiride alone.

Beginning 70/30 insulin before supper successfully restored the specified level of control in most cases, although the percentage was higher when glimepiride was

continued. More specifically, 81% of the subjects using insulin alone and 95% of those using combined therapy reported reaching the 120 mg/dl FBG target level. The subjects in both groups who completed the study had mean FPG close to 140 mg/dl, as expected, and mean HbA<sub>1c</sub> values (7.7 and 7.6%) more than 2% below those at baseline. These values compare favorably to the American Diabetes Association's targets for acceptable control. The two groups gained similar amounts of weight during treatment with insulin, ~4 kg, and blood pressure did not change. Serum triglycerides improved similarly in each group. HDL cholesterol values improved slightly more with insulin alone ( $P < 0.05$ ).

Continuing glimepiride while using this algorithm for starting insulin offered two advantages. First, glucose declined more rapidly in the first 8 weeks and without the temporary worsening of control that was evident in the insulin-only group. Probably related to the rate of improvement, there was a clear between-group difference in the discontinuation rate: 15% of subjects taking insulin alone did not complete the study, compared with only 3% of combined therapy subjects. In addition, ~40% less insulin was needed with combined therapy than with insulin alone to achieve the same FPG levels. Fewer subjects continuing with glimepiride (6% compared with 14%) needed >100 U/day, a dosage that requires more than one injection with a 100-U syringe. There was, however, no decrease in the increment of serum insulin concentrations with combined therapy compared with insulin alone.

The most common adverse events were symptoms compatible with hypoglycemia. As in other studies of this kind, in which subjects and investigators are encouraged to report all possible side effects, the milder hypoglycemic symptoms are difficult to interpret. An overall frequency approaching half the subjects suggests that many of the symptoms did not, in fact, result from low glucose levels. Thus, the modest excess of all such symptoms with combined therapy (51 vs. 37%) is of uncertain significance. Possibly it was related to the quicker decline of glucose when glimepiride was continued, even though low levels of glucose were not confirmed. There was no difference in symptoms compatible with moderate hypoglycemia (11% with combined therapy vs. 15% with insulin alone), and these figures seem clinically unimpressive. The most

important finding was that no serious hypoglycemia was documented.

The findings of the study are clinically relevant. Insulin is often started late because of its perceived difficulties, hazards, and ineffectiveness. This simple way of beginning insulin, slowly increasing doses of 70/30 insulin before supper based on self-testing of FBG at home, was safe and effective for obese patients with uncontrolled hyperglycemia. Target values for FBG were routinely achieved. Continuing glimepiride prevented the tendency for hyperglycemia to worsen when the oral agent was discontinued. The findings may encourage earlier and more systematic use of insulin.

Several modifications of the protocol might be appropriate in clinical practice. First, while 70/30 insulin taken before the evening meal was successful for obese patients in this and a previous study (6), NPH insulin at bedtime is more appropriate for less obese patients, for whom its absorption pattern may better match the overnight need for insulin (5,7,8,16). Second, once the initial target level for glucose is achieved, insulin dosage could, in some cases, be further increased, in an attempt to secure even better control (6,7). Third, secondary failure of evening-insulin therapy should be anticipated, along with the eventual need for two injections of insulin for many patients.

Finally, there is the question of dosage and costs. The dose of glimepiride used in this study, 8 mg twice daily, has recently been shown to be well above the maximally effective dose (13). For most patients, 4 mg taken once daily should be equally effective. The current average wholesale price for 100 × 4 mg glimepiride tablets is \$69.10, and that for a 10-ml vial of 70/30 insulin is \$18.91. At those prices, 73 U of insulin daily costs \$1.38, compared with \$1.62 daily for 49 U of insulin plus 4 mg glimepiride. Both regimens are inexpensive compared with many treatments, and the combined regimen costs only 23 cents/day more.

In summary, this multicenter trial showed the efficacy of evening-insulin therapy in a common clinical situation. It demonstrated that, for obese patients not responding to full doses of glimepiride, slowly titrating supertime 70/30 insulin based on patient-measured FBG safely restores acceptable glycemic control either in combination with continued glimepiride or by itself. However, combined therapy restored glycemic control more rapidly and with lower doses of insulin. Combined

therapy with glimepiride plus supertime 70/30 insulin is a safe effective treatment for obese patients with type 2 diabetes not well controlled by a sulfonylurea alone.

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