

# Glycemic Control With Diet, Sulfonylurea, Metformin, or Insulin in Patients With Type 2 Diabetes Mellitus

## Progressive Requirement for Multiple Therapies (UKPDS 49)

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ONE OF THE MAIN GOALS OF treating patients with type 2 diabetes mellitus is to produce near-normal glucose levels to prevent the development of diabetic complications. The Diabetes Control and Complications Trial<sup>1</sup> and Stockholm studies<sup>2</sup> in white patients with type 1 diabetes mellitus, and the Kumamoto study<sup>3</sup> in nonobese Japanese patients with type 2 diabetes and the UK Prospective Diabetes Study (UKPDS)<sup>4</sup> indicate that improved blood glucose control will delay the progress of microvascular complications. An epidemiological study of Pima Indians suggested that when the fasting plasma glucose (FPG) level is less than 7.8 mmol/L (140 mg/dL), the risk of developing microvascular complications is lower.<sup>5</sup> This finding was corroborated by a similar study in whites with 2-hour oral FPG tolerance data.<sup>6</sup>

More recent studies have shown the risk of retinopathy to increase at FPG levels between 6.4 and 7.6 mmol/L (115-137 mg/dL) in Pima Indians,<sup>7</sup> between 6.0 and 7.2 mmol/L (108-130 mg/dL) in Egyptians,<sup>8</sup> and between 6.0 and 6.7 mmol/L (108-121 mg/dL) in a US population sample.<sup>9</sup> The level of glycosylated hemoglobin A<sub>1c</sub> (HbA<sub>1c</sub>) that is equivalent to this level of hypergly-

**Context** Treatment with diet alone, insulin, sulfonylurea, or metformin is known to improve glycemia in patients with type 2 diabetes mellitus, but which treatment most frequently attains target fasting plasma glucose (FPG) concentration of less than 7.8 mmol/L (140 mg/dL) or glycosylated hemoglobin A<sub>1c</sub> (HbA<sub>1c</sub>) below 7% is unknown.

**Objective** To assess how often each therapy can achieve the glycemic control target levels set by the American Diabetes Association.

**Design** Randomized controlled trial conducted between 1977 and 1997. Patients were recruited between 1977 and 1991 and were followed up every 3 months for 3, 6, and 9 years after enrollment.

**Setting** Outpatient diabetes clinics in 15 UK hospitals.

**Patients** A total of 4075 patients newly diagnosed as having type 2 diabetes ranged in age between 25 and 65 years and had a median (interquartile range) FPG concentration of 11.5 (9.0-14.4) mmol/L [207 (162-259) mg/dL], HbA<sub>1c</sub> levels of 9.1% (7.5%-10.7%), and a mean (SD) body mass index of 29 (6) kg/m<sup>2</sup>.

**Interventions** After 3 months on a low-fat, high-carbohydrate, high-fiber diet, patients were randomized to therapy with diet alone, insulin, sulfonylurea, or metformin.

**Main Outcome Measures** Fasting plasma glucose and HbA<sub>1c</sub> levels, and the proportion of patients who achieved target levels below 7% HbA<sub>1c</sub> or less than 7.8 mmol/L (140 mg/dL) FPG at 3, 6, or 9 years following diagnosis.

**Results** The proportion of patients who maintained target glycemic levels declined markedly over 9 years of follow-up. After 9 years of monotherapy with diet, insulin, or sulfonylurea, 8%, 42%, and 24%, respectively, achieved FPG levels of less than 7.8 mmol/L (140 mg/dL) and 9%, 28%, and 24% achieved HbA<sub>1c</sub> levels below 7%. In obese patients randomized to metformin, 18% attained FPG levels of less than 7.8 mmol/L (140 mg/dL) and 13% attained HbA<sub>1c</sub> levels below 7%. Patients less likely to achieve target levels were younger, more obese, or more hyperglycemic than other patients.

**Conclusions** Each therapeutic agent, as monotherapy, increased 2- to 3-fold the proportion of patients who attained HbA<sub>1c</sub> below 7% compared with diet alone. However, the progressive deterioration of diabetes control was such that after 3 years approximately 50% of patients could attain this goal with monotherapy, and by 9 years this declined to approximately 25%. The majority of patients need multiple therapies to attain these glycemic target levels in the longer term.

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cemia is below 7.0% when measured by a high-performance liquid chromatographic assay with a normal range of 4.5% to 6.2%, and this is in accord with the UKPDS, which showed that the intensively treated group with HbA<sub>1c</sub> levels of 7% had 25% less incidence of microvascular end points than those with HbA<sub>1c</sub> levels of 7.9%.<sup>4</sup>

Treatment with diet, insulin, sulfonylurea, or metformin is known to improve glycemia,<sup>10</sup> but how often these therapies can attain glycemic target levels set by the American Diabetes Association<sup>11</sup> of FPG levels less than 7.8 mmol/L (140 mg/dL) or HbA<sub>1c</sub> below 7.0% in patients with type 2 diabetes has not been formally studied. The UKPDS recruited patients newly diagnosed as having diabetes, who are likely to be representative of newly presenting type 2 diabetes in the healthy population, directly from primary care physicians in 23 centers.<sup>12</sup> All were initially treated by diet alone, with subsequent randomization to continuing with diet alone, or with sulfonylurea, metformin, or insulin therapy. Since type 2 diabetes is characterized by steady deterioration of glucose control due to progressive  $\beta$ -cell dysfunction,<sup>13</sup> it becomes increasingly more difficult to attain near-normal glycemic control target levels. We report the proportion of patients with newly diagnosed type 2 diabetes who could attain these target levels with each of the agents as monotherapy after 3, 6, and 9 years of treatment, or conversely required more than 1 agent (ie, multiple therapies) to attain target levels.

## METHODS

### Patients

A total of 4075 patients newly diagnosed as having type 2 diabetes, aged 25 to 65 years inclusive, were recruited between 1977 and 1991 in the first 15 UKPDS centers established.<sup>12</sup> The remaining 1027 UKPDS patients were from the last 8 centers whose protocol did not include the randomization to metformin. The diagnostic criterion was FPG concentration higher than 6.0 mmol/L (108 mg/dL) on 2 occasions. The median (interquartile

range) FPG was 11.5 (9.0-14.4) mmol/L [207 (162-259 mg/dL)] and HbA<sub>1c</sub> was 9.1% (7.5%-10.7%). Of these patients, approximately 10% had positive test results for the islet cell antibody and/or glutamic acid decarboxylase antibody.<sup>14</sup> The mean (SD) age of the patients was 53 (9) years with a body mass index (BMI) of 29 (6) kg/m<sup>2</sup>. Eighty-one percent of the patients were white, 10% Asian-Indian, and 9% Afro-Caribbean. Fifty-five percent had presented to their general practitioners with symptoms due to hyperglycemia, 13% because of an infection, 2% following detection of clinical complications, and 30% were asymptomatic and had been diagnosed at a routine screening evaluation (eg, a life insurance medical examination). The FPG levels at diagnosis for these groups with different clinical presentations were median (interquartile range) 12.2 (9.5-15.2) mmol/L [220 (171-274) mg/dL], 11.3 (9.0-14.0) mmol/L [204 (162-252) mg/dL], 12.0 (8.8-14.4) mmol/L [216 (159-261) mg/dL], and 9.9 (8.1-12.6) mmol/L [178 (146-227) mg/dL], respectively, and HbA<sub>1c</sub> levels were 9.8% (8.2%-11.2%), 9.2% (7.8%-10.5%), 9.0% (7.5%-10.3%), and 8.0% (6.8%-9.7%), respectively.

All patients were initially prescribed, by a dietitian, a low-fat, high-carbohydrate, high-fiber diet. After 3 months on this diet, patients were stratified into 1 of the following therapies according to the mean of FPG concentration taken on 3 separate days: (1) those with an FPG concentration higher than 15 mmol/L (270 mg/dL), or with continued symptoms due to hyperglycemia, termed *primary diet failure* were randomized to either sulfonylurea (chlorpropamide or glyburide) or insulin; obese patients (>120% ideal body weight) were also randomized to monotherapy with metformin; (2) asymptomatic patients with FPG concentrations of 6 to 15 mmol/L (108-270 mg/dL) inclusive, termed *main randomization*, allocated as above but with randomization to continuing on diet therapy alone as an additional option, termed *conventional therapy*; (3) those with FPG con-

centrations of less than 6 mmol/L (108 mg/dL) who initially were not randomized but were maintained on diet alone, termed *diet satisfactory*. If the mean of 3 consecutive FPG values in patients in this latter group increased to more than 6 mmol/L (108 mg/dL) or symptoms due to hyperglycemia developed, they were randomized to an allocated therapy termed *delayed randomization* as in the main randomization above. Computer-generated randomization schedules were used, blocked by center, to ensure appropriate numbers in each allocation.

Patients were seen at clinic visits every 3 months with the aim of achieving an FPG level of less than 6 mmol/L (108 mg/dL) with the allocated therapies, increasing to maximum doses of sulfonylurea or metformin (chlorpropamide 500 mg/d, glyburide 20 mg/d, and metformin 2550 mg/d). The initial insulin regimen consisted of a once-daily dose of long-acting or isophane insulin. If the daily dose was above 14 U or if premeal or prebedtime FPG concentration was higher than 7 mmol/L (126 mg/dL), regular insulin was added to the regimen. Larger doses of insulin were used when FPG concentration was higher than 6 mmol/L (108 mg/dL). The median insulin doses at 6 and 9 years from diagnosis of type 2 diabetes were 28 U and 34 U, respectively. At 9 years, the median dose was 24 U in nonobese and 53 U in obese subjects (BMI, <25 and >35 kg/m<sup>2</sup>, respectively). If hypoglycemia occurred, the doses were reduced. Although patients initially were treated with a basal insulin supply from long-acting insulin, if home blood glucose monitoring or HbA<sub>1c</sub> levels were unsatisfactory, patients (44%) were transferred to mixtures of long- and short-acting insulin or a twice-daily mixture at 9 years. When protocol-defined marked hyperglycemia, namely an FPG concentration higher than 15 mmol/L (270 mg/dL), or symptoms due to hyperglycemia occurred despite maximal doses, additional therapy was added. Metformin was then added to maximum sulfonylurea doses or sulfonylurea was added to maximum metformin. This article evaluates the proportion

of patients who, while continuing their allocated monotherapy, could achieve FPG concentrations of less than 7.8 mmol/L (140 mg/dL) or HbA<sub>1c</sub> levels below 7% or 8% at 3, 6, and 9 years after allocation to therapy. The loss to follow-up in the study was 4%. The analyses at each 3-year interval were of patients who attended, excluding those who had died, who were lost to follow-up, or who had no data available for a particular visit.

An amendment was made to the protocol in April 1990 to assess the effect of the early addition of metformin to sulfonylurea therapy in an attempt to maintain improved blood glucose control in the patients allocated to sulfonylurea. Patients who were asymptomatic, were taking maximal doses of their allocated sulfonylurea therapy, and who had FPG concentrations of 6 mmol/L (108 mg/dL) or higher but less than 15 mmol/L (270 mg/dL) were randomly allocated to take metformin in addition to sulfonylurea or to continue with sulfonylurea alone, unless protocol-defined marked hyperglycemia developed when metformin was added.<sup>15</sup> The addition of metformin to sulfonylurea in these patients reduced the FPG concentration by 1.0 mmol/L (18 mg/dL) and HbA<sub>1c</sub> by 0.4% compared with the corresponding group taking sulfonylurea alone. Patients taking combined therapy with sulfonylurea and metformin who developed hyperglycemia were transferred to insulin therapy.

Levels of FPG were measured in each center at each visit. A monthly trilevel quality assurance scheme run by the central laboratory ensured consistency between centers with a 4% coefficient of variation. Blood and urine samples were taken annually for determination of HbA<sub>1c</sub>, plasma lipids and insulin, and urine albumin.<sup>16</sup>

Levels of HbA<sub>1c</sub> were measured in the central laboratory on heparinized whole blood samples transported overnight at 4°C. Since 1989, HbA<sub>1c</sub> has been assayed by high-performance liquid chromatography on a Bio-Rad Diamat Automated Analyser (Bio-Rad Laboratories, Hemel Hempstead, England) with a nor-

mal range in patients from age 25 to 65 years of 4.5% to 6.2%,<sup>16</sup> which compares with 4.0% to 6.0% quoted by the American Diabetes Association criteria.<sup>11</sup> Levels of HbA<sub>1c</sub> were measured by gel electrophoresis between 1979 and 1984 and by electroendosmosis between 1984 and 1989 (Corning, Halstead, England). Comparability across time was ensured by appropriate statistical techniques.<sup>17</sup>

### Statistical Analyses

In each baseline FPG stratification, the proportions of patients allocated to each therapy (A%) were taken to be representative of all patients in that randomization. The proportion of patients who at each time point were taking the randomized therapy alone was calculated (B%), and within that group the proportion who at each time point had either an FPG concentration of less than 7.8 mmol/L (140 mg/dL) (C%) or HbA<sub>1c</sub> level below 7.0% (D%) was calculated. The product of (A × B × C) or (A × B × D) indicated the proportion of patients within that stratification who maintained FPG control better than these criteria.

For statistical analyses, patients who refused their allocated therapy and continued on diet alone were included in the monotherapy group to which they had been allocated. The proportion of patients with FPG concentrations of less than 7.8 mmol/L (140 mg/dL), of 7.8 to less than 10 mmol/L (140-180 mg/dL), and 10 mmol/L (180 mg/dL) or higher and HbA<sub>1c</sub> levels below 7% at baseline who achieved the target levels was evaluated. Those who continued to have FPG concentrations of less than 6 mmol/L (108 mg/dL) on diet therapy alone and were not randomized (8%, 5%, and 4% at 3, 6, and 9 years, respectively) were excluded from the analysis at each time point.

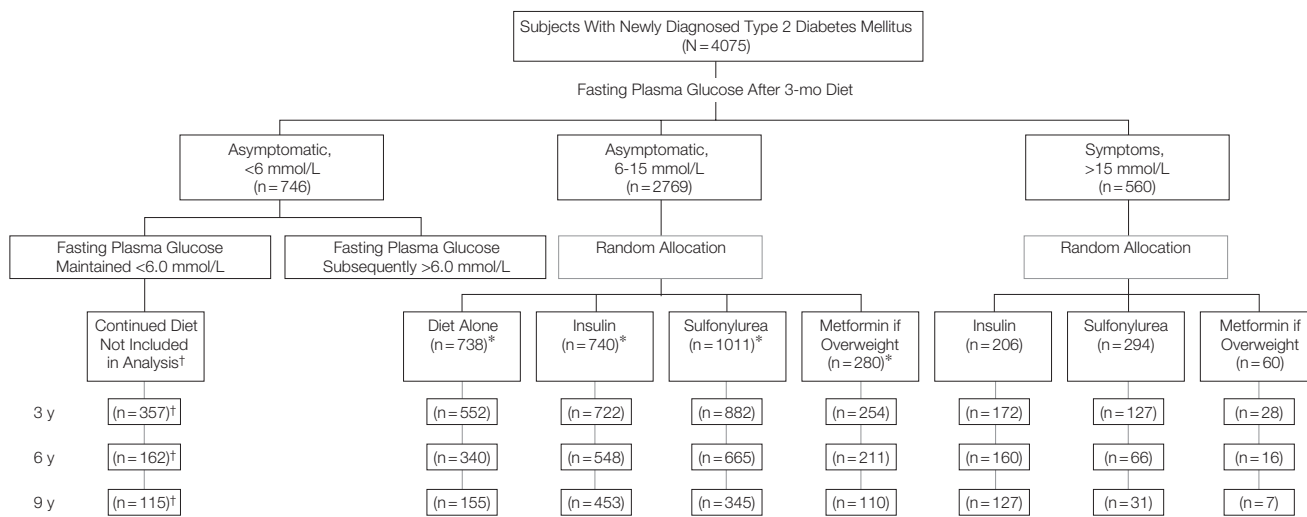
As an example, in the main randomization group after 3 years of follow-up (66% of all patients) in those allocated to chlorpropamide, 97% had continued to take sulfonylurea alone, and of these, 62% had FPG concentrations of less than 7.8 mmol/L (140 mg/dL). Thus

$0.66 \times 0.97 \times 0.62$  or 40% was the proportion of the UKPDS population represented by this group who, when treated with sulfonylurea alone for 3 years, attained an FPG concentration of less than 7.8 mmol/L (140 mg/dL). This calculation was also performed for the other stratifications, primary diet failure group (14% of all patients), and delayed randomization group (12% of all patients at 3 years). By combining these data it was possible to estimate the proportion of the total number of newly diagnosed patients with type 2 diabetes who, when treated by this monotherapy, could attain these target levels. Conversely, the remainder required an additional agent (ie, multiple therapies).

The randomization to continuing with sulfonylurea alone or to the addition of metformin with the protocol amendment, introduced in 1990 and described above, occurred in 13%, 47%, and 86% of the main randomization group of patients initially allocated to sulfonylurea by 3, 6, and 9 years, respectively. Similarly, 4%, 6%, and 19% of the primary diet failure group and 4%, 12%, and 24% of the delayed randomization group were included in this randomization. For the assessment of the response to sulfonylurea alone, proportions were adjusted to allow for the randomization of some sulfonylurea-treated patients to additional metformin therapy. In subjects who were eligible for this randomization, we assessed the proportion who, at 3 years after allocation to additional metformin, attained the glycemic targets when remaining on the allocated therapy.

Logistic regression analysis was performed using SAS<sup>18</sup> software to assess whether the degree of glycemia, age, ethnic group, sex, measures of obesity, plasma triglycerides, or mode of presentation (symptomatic or secondary to complications or identification by screening) predicted the probability of failing to achieve the target levels for HbA<sub>1c</sub> or FPG. Analysis was also done to assess the requirement for multiple therapies as a result of failing to attain the target levels, and how these variables interacted with the therapy al-

**Figure 1.** Glucose Stratification at Entry and Randomization to Different Therapies During the UK Prospective Diabetes Study



For subjects marked with an asterisk, numbers changed with duration of the study since those with fasting plasma glucose levels of less than 6 mmol/L (108 mg/dL) after 3-month diet progressively become higher than 6.0 mmol/L (108 mg/dL) and were randomized to the different therapy options. Others were removed following death or loss to follow-up. The numbers in each group are those included in the cohorts analyzed at 3, 6, and 9 years. Those marked with a dagger remained less than 6.0 mmol/L (108 mg/dL) and are not included in the analysis. To convert millimoles per liter to milligrams per deciliter, multiply by 18.

**Table 1.** Proportion of Patients Who Attain Goals\*

Therapy	Hemoglobin A <sub>1c</sub> <7.0%			Fasting Plasma Glucose <7.8 mmol/L		
	3 Years	6 Years	9 Years	3 Years	6 Years	9 Years
<b>Normal weight and overweight patients</b>						
Diet	25 (24-27)	12 (11-13)	9 (8-10)	19 (18-20)	11 (10-12)	8 (7-9)
Insulin	47 (46-49)	37 (35-38)	28 (26-29)	52 (50-54)	48 (46-50)	42 (40-44)
Chlorpropamide	53 (52-55)	39 (37-41)	28 (27-30)	51 (49-52)	39 (37-40)	28 (26-29)
Glyburide	47 (45-48)	29 (28-31)	20 (18-21)	41 (39-42)	27 (25-28)	20 (19-22)
Sulfonylurea	50 (48-52)	34 (33-36)	24 (22-26)	46 (44-47)	33 (31-34)	24 (23-26)
<b>Overweight patients</b>						
Diet	23 (21-25)	12 (10-13)	11 (10-13)	18 (16-20)	9 (8-11)	10 (9-12)
Insulin	34 (32-36)	37 (34-39)	24 (22-27)	44 (41-46)	41 (39-43)	38 (34-39)
Chlorpropamide	51 (49-53)	33 (31-35)	20 (18-22)	47 (45-50)	33 (31-36)	19 (17-21)
Glyburide	40 (38-42)	23 (21-25)	22 (20-25)	34 (32-37)	18 (17-20)	23 (21-26)
Sulfonylurea	45 (43-48)	28 (26-30)	21 (19-23)	41 (38-43)	26 (24-28)	21 (19-23)
Metformin	44 (42-46)	34 (32-37)	13 (11-15)	39 (36-41)	31 (29-33)	18 (16-20)

\*Values are proportions (95% confidence intervals) expressed as percentages. To convert fasting plasma glucose to milligrams per deciliter, multiply by 18.

locations. When continuous variables were included in the models, these were transformed so that 1 unit equated to a clinically relevant change: age, 1 unit = 10 years; BMI, 1 unit = 5 kg/m<sup>2</sup>; FPG, 1 unit = 2 mmol/L (36 mg/dL); HbA<sub>1c</sub>, 1 unit = 2%; waist circumference, 1 unit = 10 cm; plasma triglycerides, 1 unit = 1 mmol/L (89 mg/dL). For waist measurements the values were ad-

justed for the effect of sex; P ≥ .05 was considered not significant.

### RESULTS

FIGURE 1 shows, in outline, the stratification and randomization to different therapies of patients within the UKPDS. Further details are given in previous publications.<sup>12,13,19,20</sup> Numbers of patients in each therapy group in co-

horts at 3, 6, and 9 years included in the analysis are shown.

### Proportions Attaining Goals

By 6 years, only 5% allocated to sulfonylurea were able to maintain FPG concentrations of less than 6 mmol/L (108 mg/dL). TABLE 1 and FIGURE 2 summarize the results for 3, 6, and 9 years for HbA<sub>1c</sub> levels below 7.0% and FPG concentrations of less than 7.8 mmol/L (140 mg/dL) for patients allocated and remaining on allocated monotherapy. It is apparent that by 3 years, less than 55% of patients who had been randomized to any single pharmacological therapy could maintain FPG concentrations of less than 7.8 mmol/L (140 mg/dL) or HbA<sub>1c</sub> levels below 7.0%. However, each therapeutic agent, given as a monotherapy, approximately doubled the proportion of patients who could attain HbA<sub>1c</sub> levels below 7% compared with a policy of diet alone (conventional therapy). By 9 years less than 25% of patients could maintain FPG levels of less than 7.8 mmol/L (140 mg/dL) or HbA<sub>1c</sub> levels below 7.0% with sulfonylurea alone. Patients allocated to insulin showed a similar response over the first 6 years, but by 9 years almost twice as many achieved the FPG

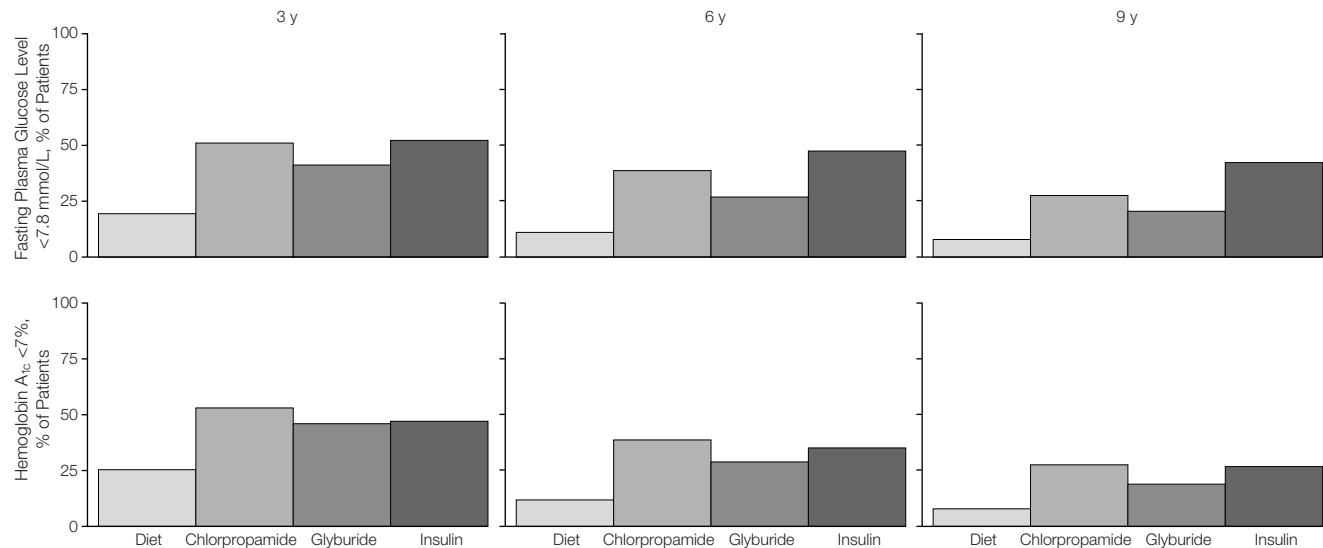
target level as those taking sulfonylurea alone (42% vs 24%, respectively). However, the response for HbA<sub>1c</sub> after 9 years was similar for both therapies (for HbA<sub>1c</sub> <7%: 28% vs 24%, respectively). Pa-

tients taking chlorpropamide consistently achieved the target levels more often than those taking glyburide.

Overweight patients allocated to metformin (Table 1) showed a similar re-

sponse to overweight patients allocated to sulfonylurea, with 39% of those taking metformin achieving FPG concentrations of less than 7.8 mmol/L (140 mg/dL) compared with 41% tak-

**Figure 2.** Proportions of Patients in Each Therapy Allocation



Values are for patients who remained receiving monotherapy and achieved different control targets after 3, 6, and 9 years.

**Table 2.** Univariate Logistic Regression Analysis of Predictive Factors\*

Variable	Hemoglobin A <sub>1c</sub> >7%		Fasting Plasma Glucose >7.8 mmol/L			
	Odds Ratio (95% CI)	P Value	Odds Ratio (95% CI)	P Value		
Age per 10 y	0.72 (0.64-0.81)	<.001	0.75 (0.67-0.84)	<.001		
Hemoglobin A <sub>1c</sub> per 2%	1.40 (1.25-1.57)	<.001	1.11 (0.99-1.24)	>.05		
Fasting plasma glucose per 2 mmol/L†	1.20 (1.12-1.30)	<.001	1.12 (1.04-1.20)	.003		
Body mass index per 5 kg/m <sup>2</sup>	1.25 (1.04-1.50)	.02	1.48 (1.24-1.78)	<.001		
Waist circumference per 10 cm‡	1.09 (1.01-1.18)	.02	1.16 (1.08-1.25)	<.001		
Plasma triglyceride per 1 mmol/L	1.33 (1.10-1.61)	.003	1.34 (1.11-1.61)	.002		
Positive result for islet cell antibody and glutamic acid decarboxylase antibody	1.29 (0.94-1.78)	>.05	0.88 (0.64-1.20)	>.05		
	No. of Subjects		No. of Subjects			
Conventional vs Intensive therapy	1589	0.64 (0.51-0.81)	<.001	1651	0.39 (0.31-0.49)	<.001
Insulin	936	0.76 (0.59-0.99)	.04	974	0.36 (0.27-0.47)	<.001
Sulfonylurea	1027	0.54 (0.42-0.70)	<.001	1063	0.41 (0.32-0.54)	<.001
Metformin§	343	0.61 (0.40-0.94)	.03	361	0.55 (0.36-0.83)	.005
Insulin§	384	0.88 (0.58-1.32)	>.05	406	0.59 (0.40-0.89)	.01
Sulfonylurea§	441	0.58 (0.39-0.86)	.007	453	0.66 (0.44-0.97)	.03

\*After 3 months' diet for likelihood of requiring multiple therapies since glycemic goals were not achieved at 3 years after allocation in 1775 patients. CI indicates confidence interval.

†To convert fasting plasma glucose to milligrams per deciliter divide by 0.05551.

‡Adjusted for sex differences.

§Values are for overweight subjects only.

ing sulfonylurea at 3 years, and 18% compared with 21%, respectively, after 9 years. In relation to the HbA<sub>1c</sub> target levels, metformin compared well with sulfonylurea at 6 years (34% vs 39% for HbA<sub>1c</sub> <7%, respectively, *P* = .46), but not as well by 9 years (13% vs 27%; *P* < .001).

**Univariate Analysis of Predictors of Requirement for Additional Therapy**

TABLE 2 shows the results of a logistic regression analysis for 3 years of follow-up of the probability of requiring multiple therapies due to HbA<sub>1c</sub> levels of 7.0% or above or FPG concentrations of 7.8 mmol/L (140 mg/dL) or higher at 3 years. In this univariate analysis, a young age at diagnosis, increased baseline obe-

sity (assessed as either BMI or waist circumference), increased baseline glycaemia, and plasma triglycerides were all significantly associated with the likelihood of requiring multiple therapies. The islet cell antibody or glutamic acid decarboxylase status of the patients was not associated with either of the targets. There were no significant associations with ethnic or sex differences, nor with reasons for presentation.

Randomization to intensive therapy with insulin or sulfonylurea gave less likelihood of requiring additional therapy to attain an HbA<sub>1c</sub> level below 7%, or an FPG concentration of less than 7 mmol/L (126 mg/dL), compared with conventional therapy with diet alone (Table 2). In overweight patients randomized to metformin

therapy, the likelihood of requiring additional therapy was also less compared with conventional therapy (Table 2). For overweight patients allocated to sulfonylurea compared with conventional therapy, the likelihood was also lower for an HbA<sub>1c</sub> level below 7%, and for an FPG concentration of less than 7.8 mmol/L (140 mg/dL) while for those allocated to insulin, the likelihood was significantly lower for an FPG concentration of less than 7.8 mmol/L (140 mg/dL), but lower was not significantly different for an HbA<sub>1c</sub> level below 7% (Table 2). FIGURE 3 shows these odds ratios (ORs) and 95% confidence intervals (CIs) for the therapy comparisons for HbA<sub>1c</sub> levels below 7%.

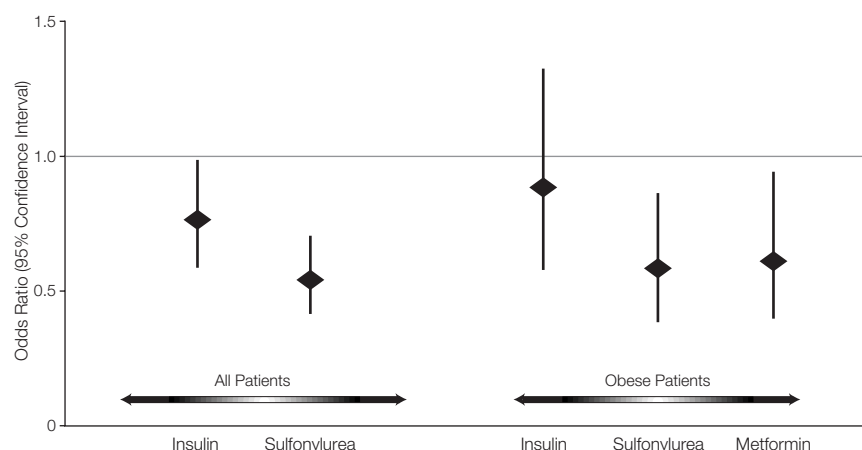
**Multivariate Analysis of Response to Therapies**

A multivariate logistic regression analysis for intensive therapy with insulin or sulfonylurea compared with conventional therapy was performed in relation to the requirement for additional therapy at 3 years, in which covariates for inclusion in the model were those significant in the univariate analysis, with a stepwise selection process to identify the final model.

Randomization to intensive therapy gave a lower likelihood of requiring additional therapy for HbA<sub>1c</sub> levels below 7% (OR, 0.55; 95% CI, 0.43-0.69; *P* < .001), and for FPG concentrations of less than 7.8 mmol/L (140 mg/dL) (OR, 0.34; 95% CI, 0.27-0.44; *P* < .001) (TABLE 3). In relation to the FPG goal, therapy allocation was the most important factor entering into the model before other covariates. Higher baseline levels of FPG or HbA<sub>1c</sub> gave a greater likelihood of requiring multiple therapies to achieve the required levels after 3 years in both models. Younger age at diagnosis and greater obesity (BMI) were also associated with greater requirement for multiple therapies. Neither plasma triglycerides nor islet cell antibody and/or glutamic acid decarboxylase status were predictive for multiple therapies in these models.

In a similar analysis comparing insulin with sulfonylurea, insulin therapy

**Figure 3.** Univariate Analysis of Multiple Therapies to Achieve HbA<sub>1c</sub> Below 7%



The patients allocated to and remaining on diet alone formed the reference group for the comparison with insulin, sulfonylurea, and metformin. When the 95% confidence interval about the odds ratio is less than 1.0, that therapy has a significantly decreased requirement for additional therapy to achieve HbA<sub>1c</sub> of less than 7%.

**Table 3.** Conventional vs Intensive Therapy With Insulin or Sulfonylurea\*

Variable	Hemoglobin A <sub>1c</sub> <7% (n = 1589)			Fasting Plasma Glucose <7.8 mmol/L (n = 1651)		
	Odds Ratio (95% CI)	Order in Model	P Value	Odds Ratio (95% CI)	Order in Model	P Value
Intensive vs conventional therapy	0.55 (0.43-0.69)	3	<.001	0.34 (0.27-0.44)	1	<.001
Hemoglobin A <sub>1c</sub>	1.45 (1.28-1.64)	1	<.001	...	...	...
Age	0.73 (0.65-0.83)	2	<.001	0.70 (0.62-0.79)	2	<.001
Body mass index	0.55 (0.43-0.70)	4	.02	1.25 (1.13-1.40)	3	<.001
Fasting plasma glucose	...	...	...	1.15 (1.06-1.24)	4	<.001

\*Stepwise logistic regression model for likelihood of requiring multiple therapies as glycemic goals were not achieved at 3 years after allocation. CI indicates confidence interval; ellipses, variable not included in model.

gave an increased likelihood of requiring additional therapy to achieve HbA<sub>1c</sub> levels below 7% (OR, 1.36; 95% CI, 1.08-1.72; *P* = .01) after inclusion of baseline HbA<sub>1c</sub> level (OR, 1.35; 95% CI, 1.18-1.53; *P* < .001), age (OR, 0.74; 95% CI, 0.65-0.86; *P* < .001), and BMI (OR, 1.15; 95% CI, 1.02-1.30; *P* < .001) in the model.

In multivariate models in obese patients comparing metformin with diet therapy, metformin reduced the likelihood of requiring multiple therapies (*n* = 343) with HbA<sub>1c</sub> levels below 7% (OR, 0.44; 95% CI, 0.27-0.72; *P* < .001), with baseline HbA<sub>1c</sub> (OR, 1.96; 95% CI, 1.40-2.75; *P* ≤ .005), high plasma triglycerides (OR, 2.01; 95% CI, 1.24-3.27; *P* < .001), and young age (OR, 0.53; 95% CI, 0.39-0.72; *P* < .001) also significantly predictive.

## COMMENT

The increasing failure of monotherapy with sulfonylurea, metformin, or insulin to achieve tight glycaemic control over the first 9 years following diagnosis of type 2 diabetes is consistent with the progressive decline of  $\beta$ -cell function.<sup>13</sup> By 3 years after diagnosis of diabetes, approximately 50% of patients will need more than 1 pharmacological agent (ie, multiple therapies) because monotherapy does not achieve the target values of HbA<sub>1c</sub>, and by 9 years approximately 75% of patients will need multiple therapies to achieve FPG concentrations of less than 7.8 mmol/L (140 mg/dL) or HbA<sub>1c</sub> levels below 7%. In an intent-to-treat analysis, the efficacy of early addition of metformin therapy to maximum sulfonylurea therapy has been shown after 3 years to increase the proportion of patients achieving HbA<sub>1c</sub> levels below 7% from 21% with sulfonylurea alone to 33% with additional metformin.<sup>15</sup> It is apparent by 9 years after diagnosis that even with this combination of oral agents a substantial number, possibly the majority, of patients will need the addition of insulin therapy to obtain an HbA<sub>1c</sub> level below 7%. Since improved glucose control with insulin therapy is known to

reduce the risk of diabetes complications,<sup>4</sup> the progressive decline in  $\beta$ -cell function with greater hyperglycemia<sup>13</sup> will require considerably greater use of insulin therapy than that currently prescribed. While thiazolidinediones are an additional oral agent that can be used, in clinical practice they have similar efficacy to sulfonylurea or metformin in reducing glycemia, which usually remains supranormal,<sup>21,22</sup> and these new agents are unlikely to prevent the increasing glycemia or to postpone the need for insulin therapy for more than a few years.

Although insulin therapy was better than sulfonylurea or metformin at reducing FPG concentrations, it was not as effective in reducing HbA<sub>1c</sub> as might have been anticipated. This is partly because oral agents reduce the postprandial as well as fasting glucose level, whereas a basal insulin supply only reduced the basal glucose concentrations.<sup>23</sup> Adding soluble insulin to cover the meals can lead to hypoglycemic attacks that limit the degree to which near-normal glycemia can be attained.<sup>20</sup> According to published reports, HbA<sub>1c</sub> levels below 7% have only been achieved with high insulin doses, often well above 100 U/d, in small groups of obese patients receiving detailed attention over a short-term period.<sup>24-26</sup> In studies in fewer obese patients taking smaller insulin doses, mean HbA<sub>1c</sub> levels of 8% or above were achieved.<sup>27-29</sup> The UKPDS included patients who would not comply with a complex insulin regimen so it is thus a real-life study. While the American Diabetes Association guidelines suggest a glycaemic goal of HbA<sub>1c</sub> below 7%, monotherapies can achieve this in only a minority of patients.<sup>30</sup>

This study shows that the initial severity of diabetes, assessed by the degree of hyperglycemia, is a major factor in determining the likelihood of achieving glucose target levels, and that it is also more difficult to achieve the target levels in more obese patients. Nevertheless, the allocation to therapy with sulfonylurea, basal insulin, or metformin compared with diet alone more

than doubled the proportion of patients with type 2 diabetes who achieved the target levels. This degree of improved glucose control is clinically effective in preventing microvascular complications of diabetes.<sup>4</sup>

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Scientific truth, which I formerly thought of as fixed, as though it could be weighed and measured, is changeable. Add a fact, change the outlook, and you have a new truth. Truth is a constant variable. We seek it, we find it, our viewpoint changes, and the truth changes to meet it.

—William J. Mayo (1861-1939)