Sulfonylurea Inadequacy

Efficacy of addition of insulin over 6 years in patients with type 2 diabetes in the U.K. Prospective Diabetes Study (UKPDS 57)

ALEX WRIGHT, FRCP[1]
A.C. FELIX BURDEN, FRCP[2]
RICHARD B. PAISEY, FRCP[3]
CAROLE A. CULL, PHD[4]
RURY R. HOLMAN, FRCP[4]
FOR THE U.K. PROSPECTIVE DIABETES STUDY GROUP

OBJECTIVE — To evaluate the efficacy of the addition of insulin when maximal sulfonylurea therapy is inadequate in individuals with type 2 diabetes.

RESEARCH DESIGN AND METHODS — Glycemic control, hypoglycemia, and body weight were monitored over 6 years in 826 patients with newly diagnosed type 2 diabetes in 8 of 23 U.K. Prospective Diabetes Study (UKPDS) centers that used a modified protocol. Patients were randomly allocated to a conventional glucose control policy, primarily with diet ($n = 242$) or an intensive policy with insulin alone ($n = 245$), as in the main study. However, for patients randomized to an intensive policy with sulfonylurea ($n = 339$), insulin was added automatically if the fasting plasma glucose remained >108 mg/dl (6.0 mmol/l) despite maximal sulfonylurea doses.

RESULTS — Over 6 years, ~53% of patients allocated to treatment with sulfonylurea required additional insulin therapy. Median HbA_{1c} in the sulfonylurea ± insulin group was significantly lower (6.6%, interquartile range [IQR] 6.0–7.6) than in the group taking insulin alone (7.1%, IQR 6.2–8.0; $P = 0.0066$), and significantly more patients in the sulfonylurea ± insulin group had an HbA_{1c} <7% (47 vs. 35%, respectively; $P = 0.011$). Weight gain was similar in the intensive therapy groups, but major hypoglycemia occurred less frequently over all in the sulfonylurea (± insulin) group compared with the insulin alone group (1.6 vs. 3.2% per annum, respectively; $P = 0.017$).

CONCLUSIONS — Early addition of insulin when maximal sulfonylurea therapy is inadequate can significantly improve glycemic control without promoting increased hypoglycemia or weight gain.

Diabetes Care 25:330–336, 2002

The U.K. Prospective Diabetes Study (UKPDS) showed that intensive control of blood glucose with sulfonylurea or insulin, and with metformin in overweight patients, substantially reduced the risk of diabetic complications (1). The intensive glucose control policy used in the first 15 UKPDS centers (Glucose Study 1) required patients to remain on their allocated monotherapy, unless fasting plasma glucose (FPG) levels increased to >15 mmol/l or hyperglycemic symptoms ensued, to evaluate specific advantages or disadvantages of individual therapies. With the realization that progressive hyperglycemia was occurring in all randomized groups (2–4) and that additional therapy might be desirable at the stage of sulfonylurea inadequacy (5) rather than sulfonylurea failure, a modified protocol (Glucose Study 2) was introduced in the last eight UKPDS centers (6). This protocol, the aim of which was to determine whether a more aggressive glucose control policy could minimize hyperglycemic progression, differed only in that insulin therapy was added immediately in patients allocated to sulfonylurea therapy if maximal doses did not maintain FPG levels <108 mg/dl (6.0 mmol/l).

A meta-analysis of randomized controlled trials (7) has shown that combining sulfonylurea and insulin therapy can improve metabolic control with significantly smaller daily doses of insulin than therapy with insulin alone and without significant change in body weight. The trials included, however, were mainly short-term, ranging from 8–16 weeks to a maximum of 1 year, and few used additional insulin at an early stage in disease progression.

We report in this study the efficacy of the addition of insulin therapy over 6 years in patients with sulfonylurea inadequacy.

RESEARCH DESIGN AND METHODS

Subjects

Between 1987 and 1991, general practitioners in the catchment areas of the eight UKPDS Glucose Study 2 hospital centers were asked to refer all patients aged 25–65 years whom they considered to have newly diagnosed diabetes. Patients with FPG levels >108 mg/dl (6.0 mmol/l) on two mornings 1–3 weeks apart, in the absence of any acute illness, were eligible for the study. Of these patients, FPG level was ≥7.8 mmol/l in 85% (6). Exclusion criteria were the same as for the other 15 UKPDS centers (6): ketonuria >0.3 mg/dl (3 mmol/l), serum creatinine >2.0 mg/dl (175 μmol/l), myocardial infarction during the previous year, current angina or heart failure, more than one major vascular event, retinopathy requiring laser treatment, malignant hypertension,

From [1]University Hospital, Birmingham, U.K.; [2]University Hospitals of Leicester, Leicester, U.K.; [3]Torbay Hospital, Torquay, Devon, U.K.; and the [4]Diabetes Trials Unit, OCDEM, University of Oxford, Oxford, U.K.
Address correspondence and reprint requests to Dr. Carole A. Cull, Diabetes Trials Unit, Radcliffe Infirmary, Woodstock Rd., Oxford OX2 6HE U.K. E-mail: carole.cull@dtu.ox.ac.uk.
Received for publication 15 March 2001 and accepted in revised form 9 October 2001.
Abbreviations: C, conventional glucose control policy; CI, chlorpropamide ± insulin; FPG, fasting plasma glucose; GI, glipizide ± insulin; IQR, interquartile range; SI, sulfonylurea ± insulin; UKPDS, U.K. Prospective Diabetes Study.
A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

uncorrected endocrine disorder, occupation that precluded insulin therapy, severe concurrent illness that would limit life or require extensive systemic treatment, and inadequate understanding and unwillingness to enter the study.

Study protocol

The 1,375 patients identified by the general practitioners were referred to UKPDS Glucose Study 2 and were prescribed a low-fat, high-carbohydrate, high-fiber diet. The patients were seen monthly by a physician and a dietitian during a 3-month run-in period. Overweight patients were advised to reduce caloric intake. After the run-in period, a mean FPG was calculated from three separate measurements made over 2 weeks. The 348 patients excluded differed from the 1,027 recruited only in that they were significantly younger (49 vs. 52 years; $P < 0.0001$). The main reason for exclusion was protocol-defined preexisting illness or chronic concurrent illness sufficient to prevent continuation in a long-term study (47%); an additional 35% of patients cited practical reasons or unwillingness to take insulin.

Of the 1,027 patients recruited, 152 could not be randomized to dietary therapy because their FPG levels were >270 mg/dl (15.0 mmol/l) or because they had hyperglycemic symptoms during the run-in period; these patients were randomized separately only to the intensive glucose control policy (Fig. 1). An additional 49 patients were not randomized because they were able to achieve FPG <108 mg/dl (6.0 mmol/l) on diet therapy alone during the run-in period and were able to maintain this level over the following 6 years. Of the remaining 826 patients analyzed in this study, 242 patients (29%) were randomized to a conventional glucose control policy, primarily with diet, whereas 339 patients (41%) were allocated to an intensive glucose control policy with sulfonylurea ± insulin (chlorpropamide 169 [20%], glipizide 170 [21%]) and 245 patients (30%) were allocated to treatment with insulin alone. A total of 90 of the 826 patients who achieved FPG <108 mg/dl during the run-in period remained on diet alone but were subsequently randomized because FPG increased to >108 mg/dl (6.0 mmol/l) after median 1.5 years (IQR 1.0–2.5) and were also followed for 6 years. Randomization was accomplished by means of centrally produced, computer-generated therapy allocations in sealed, opaque envelopes, which were numbered and opened in sequence

Conventional glucose control policy

The aim of the conventional glucose control policy was to achieve the best possible FPG on diet alone. If the FPG level increased to >270 mg/dl (15.0 mmol/l) or if hyperglycemic symptoms occurred, patients were secondarily randomized to nonintensive pharmacological treatment with chlorpropamide (28%), glipizide (28%), or insulin (44%) at doses sufficient to relieve symptoms and maintain FPG <270 mg/dl (15.0 mmol/l). In those secondarily allocated to sulfonylurea in whom the FPG level again increased to >270 mg/dl (15.0 mmol/l) or hyperglycemic symptoms occurred on maximal doses (chlorpropamide 500 mg/day, glipizide 20 mg twice daily), treatment was changed to a nonintensive insulin regimen.

Intensive glucose control policy

The aim of the intensive glucose control policy was to achieve and maintain FPG <108 mg/dl (6.0 mmol/l). Patients allocated to insulin alone were treated as in the original UKPDS protocol (1). Initially, bovine ultralente insulin was prescribed, but most patients subsequently received human ultralente insulin. For those allocated to sulfonylurea, the modified UKPDS protocol used in this Glucose Study 2 meant that ultralente insulin was added if, on maximal sulfonylurea therapy (chlorpropamide 500 mg once daily, glipizide 20 mg twice daily), the mean of three successive FPG values increased to >108 mg/dl (6.0 mmol/l). The sulfonylurea therapy was continued unchanged with the starting dose of ultralente based on the formula (FPG mmol/l − 3) × 2 units and adjusted for body weight (8); this therapy was administered once daily before the evening meal. Patients were then seen weekly or biweekly, and the insulin dose was increased as necessary to maintain FPG <108 mg/dl (6.0 mmol/l). Human soluble insulin was added before meals if preprandial home blood glucose levels remained >126 mg/dl (7.0 mmol/l). Patients who continued to refuse addition of insulin to sulfonylurea therapy were maintained on sulfonylurea monotherapy unless FPG levels increased to >270 mg/dl (15.0 mmol/l) or hyperglycemic symptoms occurred, when therapy was changed to insulin alone.

Clinical and biochemical data were collected every 3 months as described previously (1,9). Self-reported hypoglycemia was recorded and graded by the physician; major hypoglycemic episodes were defined as those requiring third party or medical assistance. HbA_{1c} was measured annually by high-performance liquid chromatography (Diamat Automated Glycosylated Hemoglobin Analyser; Bio-Rad, Hemel Hempstead, U.K.) aligned to the Diabetes Control and Complications Trial (normal range 4.5–6.2%).

Statistical analysis

Statistical analyses were performed using SAS statistical software (SAS Institute, Cary, NC) (10) on an intention-to-treat basis apart from the occurrence of hypoglycemia; data were analyzed both for patients remaining on their allocated therapy at each time point and by intention to treat. Annual mean weight and median FPG values were calculated for each patient using the results from the annual visit and those 3 months before and after. Glucose control and HbA_{1c} were assessed both cross-sectionally and in the cohort of patients with complete 6-year follow-up. Data are reported as mean (SD), geometric mean (1 SD interval), median (IQR), or as percentages. Comparisons of continuous data used two-sample Student's *t* tests or ANOVA. For nonnormally distributed data, the Wilcoxon signed-rank test or Kruskal-Wallis test was used; χ^2 tests were used for categorical variables, and when cells contained <5% of the data, Fisher's exact test was used. Throughout the study, $P < 0.05$ was considered significant. Bonferroni correction was applied when necessary to protect from type 1 error when performing multiple tests. The number of patients and the length of follow-up was insufficient to provide adequate statistical power for analysis of the clinical outcomes defined by protocol in the main study.

RESULTS — The baseline characteristics of the 826 patients in Glucose Study 2 reported herein, which differed from those in Glucose Study 1 only in that the ethnic proportions reflected the different geographical centers used, are shown in Table 1. There were no significant differences between patients allocated to chlor-

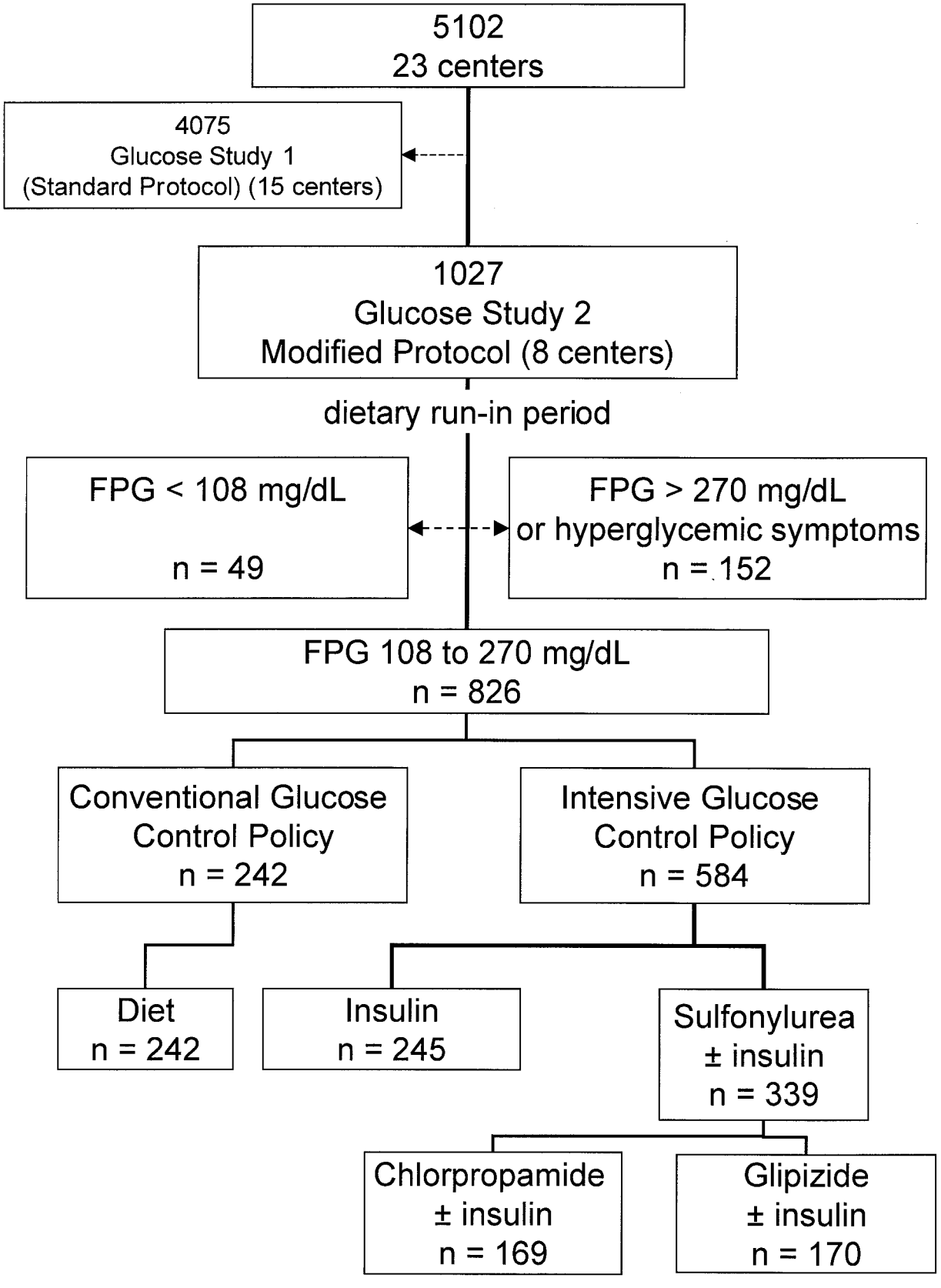

Figure 1—*Recruitment and randomization flow chart.*

Table 1—*Patient characteristics at randomization into the study*

Variable	Conventional glucose control policy	Intensive glucose control policy			All
		Insulin alone	Chlorpropamide (± insulin)	Glipizide (± insulin)	
n	242	245	169	170	826
Sex (% male)	59	60	56	63	59
Ethnic group (%)					
White Caucasian	77	80	79	77	79
Afro-Caribbean	5	4	5	5	5
Indian Asian	18	16	16	18	16
Age (years)	52 ± 9	52 ± 9	52 ± 10	52 ± 10	52 ± 9
Fasting plasma glucose (mg/dl)	149 (131–184)	151 (130–185)	149 (130–182)	149 (128–176)	149 (130–182)
HbA_{1c} (%)	7.0 (6.2–8.1)	6.9 (6.1–8.0)	6.9 (6.0–8.1)	6.9 (6.0–7.7)	6.9 (6.1–8.0)
Weight (lb)	180 ± 40	180 ± 40	176 ± 37	178 ± 37	178 ± 37
BMI (kg/m^2)	28.8 ± 5.9	29.3 ± 6.4	28.4 ± 4.9	28.5 ± 5.5	28.8 ± 5.8
Systolic blood pressure (mmHg)	132 ± 19	134 ± 21	133 ± 20	131 ± 19	132 ± 20
Diastolic blood pressure (mmHg)	80 ± 10	82 ± 11	81 ± 10	80 ± 10	81 ± 10

Data are means ± SD or median (IQR).

propamide ± insulin (CI) or to glipizide ± insulin (GI) compared with those allocated to insulin alone or to the conventional glucose control policy (*C*).

Sulfonylurea inadequacy

There was a progressive increase over 6 years (Fig. 2) in the proportion of patients with sulfonylurea inadequacy. At 6 years, 53% had required additional insulin therapy, with no significant difference between those allocated to chlorpropamide and glipizide (49 vs. 56%, $P = 0.28$) with similar proportions refusing additional insulin therapy (2.6 vs. 1.6%, $P = 0.60$). Of the patients taking sulfonylurea and insulin at 6 years, similar proportions were taking soluble insulin in addition to basal insulin (chlorpropamide 22%, glipizide 16%) as for those allocated to insulin alone (21%, $P = 0.18$).

Glycemic control

Median FPG and HbA_{1c} levels over 6 years in patients with data at each time point are shown in Fig. 3. After randomization, there was a maintained difference between patients allocated to conventional and intensive glucose control policies but no significant differences in FPG between the intensive therapy groups. However, those allocated to sulfonylurea ± insulin (SI) maintained lower HbA_{1c} levels than those on insulin alone for most of the time. Median (IQR) HbA_{1c} over 6 years (Table 2) was significantly lower for SI (6.6% [6.0–7.6]) than I (7.1 [6.2–8.0], $P = 0.0066$). There was no difference between CI (6.6 [5.9–7.6%] and GI (6.7 [6.1–7.6], $P = 0.36$). The proportion of patients with HbA_{1c} <7% at 6 years (Fig. 4) was greater in patients taking SI compared with those taking insulin alone (47 vs. 35%, $P = 0.011$) with no difference between CI or GI (48 vs. 46%, $P = 0.78$).

Median (IQR) insulin doses at 6 years were greater in the insulin alone group (0.30 U/kg [0.24–0.40]) than in the SI group (0.24 U/kg [0.16–0.40], $P = 0.0049$). In those patients achieving an HbA_{1c} <7.0%, median insulin doses were lower in the SI group (0.18 [0.14–0.40] vs. 0.28 [0.21–0.37] U/kg, $P = 0.088$) but did not reach statistical significance; there was no difference between the CI group (0.15 U/kg [0.12–0.22])

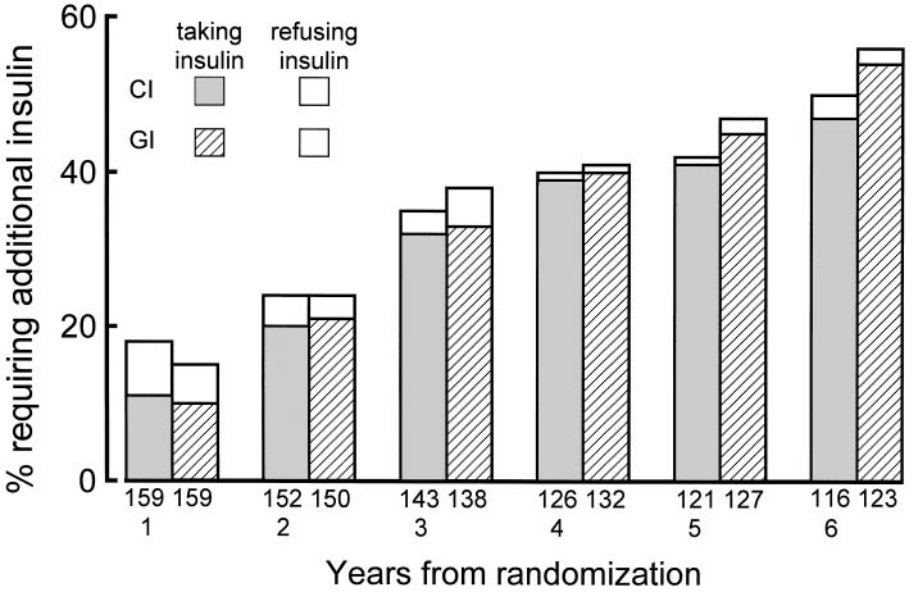

Figure 2—*Proportions of patients (%) allocated to chlorpropamide or glipizide requiring early addition of insulin each year because FPG increased to >108 mg/dl (6.0 mmol/l) despite maximal sulfonylurea doses. Those requiring but refusing additional insulin are indicated separately. The number below each column is the number of patients per year. There were no significant differences between the chlorpropamide and glipizide groups at any time point.*

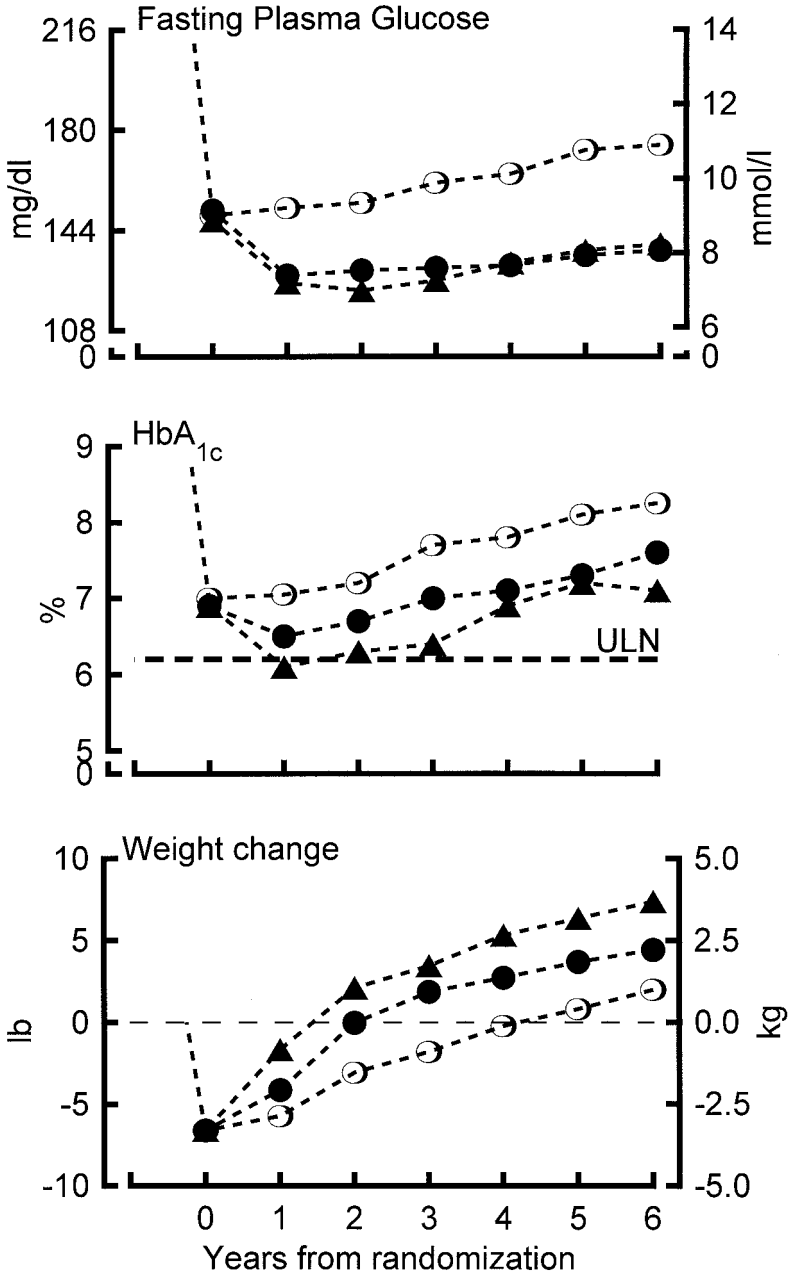

Figure 3—*Median fasting plasma glucose, HbA_{1c}, and mean change in body weight over 6-year follow-up (cross-sectional data). ○, conventional glucose control policy; ●, insulin alone; ▲, sulfonylurea ± insulin. ULN, upper limit of HbA_{1c} nondiabetic range = 6.2%.*

and the GI group (0.25 U/kg [0.16–0.40]) ($P = 0.080$). Median insulin doses in patients who did not achieve an HbA_{1c} <7.0% were also lower in the SI group (0.25 U/kg [0.17–0.38]) compared with the insulin alone group (0.31 U/kg [0.25–0.41], $P = 0.0065$).

Body weight

Patients allocated to SI or insulin alone regained their starting weight after ~2 years (Fig. 3), whereas those in the C group remained below their initial weight for between 4 and 5 years. Patients allocated to CI gained slightly more weight over 6 years (4.0 kg [6.0]) than those allocated to GI (2.8 kg [5.5], $P = 0.048$) or to insulin alone (2.0 kg [6.8], $P = 0.007$). However, these differences in weight gain between the intensive policy groups were no longer statistically significant when adjusted for the small differences in initial weight (Table 1). Weight gain was greater in all three intensive policy groups compared with the conventional therapy group (0.9 kg [6.8], $P < 0.0001$).

Hypoglycemia

Major episodes of hypoglycemia occurred less frequently over all (Table 2) in the SI group compared with the insulin alone group (1.6 vs. 3.2% per annum, $P = 0.0033$) with no significant difference between the rates in the CI and GI groups (1.8 vs. 1.4% per annum, respectively, $P = 0.56$). In those patients randomized to the CI or GI groups, the rates of major hypoglycemic episodes were similar those in the I group (5.8% [95% confidence interval 2.3–9.3] and 2.8% [0.4–5.2] per annum, respectively).

CONCLUSIONS — The addition of a basal insulin supplement when sulfonylurea monotherapy fails is now well established (11), but the introduction of insulin at the much earlier stage of sulfonylurea inadequacy (5) has not been evaluated in a long-term study. This report of the Glucose Study 2 component of the UKPDS shows that glycemic control can be significantly improved in patients with FPG levels >6.0 mmol/l despite maximal sulfonylurea therapy without promoting increased hypoglycemia or weight gain. The further reduction in HbA_{1c} by ~0.5%, as seen with SI compared with insulin alone, is beneficial, considering that the UKPDS (1) confirmed that improved glycemic control significantly reduced the risk of diabetes-related complications. The epidemiological analysis of UKPDS data (12) suggests that an 0.5% decrement in HbA_{1c} might equate to a 11.5% reduction in risk for diabetes-related complications.

The progressive nature of the hyperglycemia seen in type 2 diabetes (3) is exemplified by the evidence herein that 53% of patients with newly diagnosed diabetes treated with sulfonylurea therapy require additional treatment within 6 years to maintain FPG levels <6.0 mmol/l. A basal insulin regimen was used in this study because it is highly effective in suppressing basal hepatic glucose production (13,14). The overall improvement seen in glycemic control may reflect increased glucose-mediated release potentiated by the sulfonylureas in the setting of adequate basal insulin implementation. Insulin would seem to be the

Table 2—*HbA_{1c} over 6-year follow-up and proportion of patients (%) per annum experiencing major hypoglycemic episodes (requiring third party or medical assistance)*

	HbA_{1c}			Major hypoglycemic episodes	
Allocation	Median (IQR) (%)	*P* versus conventional glucose control policy	*P* versus insulin alone	% (95% CI) patients per annum	*P* value versus insulin alone
Conventional glucose control policy	7.6 (6.8–8.7)			0	
Intensive glucose policy control					
Insulin alone	7.1 (6.2–8.0)	<0.00001		3.4 (2.2–4.5)	
Sulfonylurea (± insulin)	6.6 (6.0–7.6)	<0.00001	0.0066	1.6 (0.9–2.2)	0.0033
Chlorpropamide (± insulin)	6.6 (5.9–7.6)	<0.00001	0.010	1.8 (0.8–2.7)	0.044
Glipizide (± insulin)	6.7 (6.1–7.6)	<0.00001	0.048	1.4 (0.6–2.2)	0.0076

natural replacement therapy to offset the progressive loss of β-cell function seen in type 2 diabetes (3).

Although there is always a concern that patients taking additional insulin will gain weight, this study indicates that the early combination of sulfonylurea and insulin does not promote weight gain over and above that seen in patients allocated to therapy with insulin alone. The slightly greater weight gain seen with CI compared with GI may be due to fluid retention associated with increased blood pressure (1). Although there may be concern about the incidence of hypoglycemic episodes in patients taking insulin, this study shows that the risk of major hypoglycemic episodes was not increased with the early addition of insulin to sulfonylurea therapy.

The decision to add insulin immediately when sulfonylurea monotherapy is inadequate, rather than alternative oral agents such as α-glucosidase inhibitors, biguanides, thiazolidinediones, or meglitinides, cannot be answered by this study because these different combinations were not compared directly. This study suggests, however, that adding insulin to sulfonylurea therapy should be considered a viable alternative to adding other oral agents when maximal doses do not maintain FPG <108 mg/dl (6.0 mmol/l).

Acknowledgments— This study was supported by major grants from the U.K. Medical Research Council; the British Diabetic Association; the U.K. Department of Health; the National Eye Institute; the National Institute of Digestive, Diabetes and Kidney Disease in the National Institutes of Health (U.S.); the British Heart Foundation; Novo-Nordisk; Bayer; Bristol Myers Squibb; Hoechst; Lilly; Lipha; and Farmitalia Carlo Erba. Other funding companies and agencies, the supervising committees, and all participating staff are listed in an earlier study (1).

We thank the patients and many NHS and non-NHS staff at the centers for their cooperation.

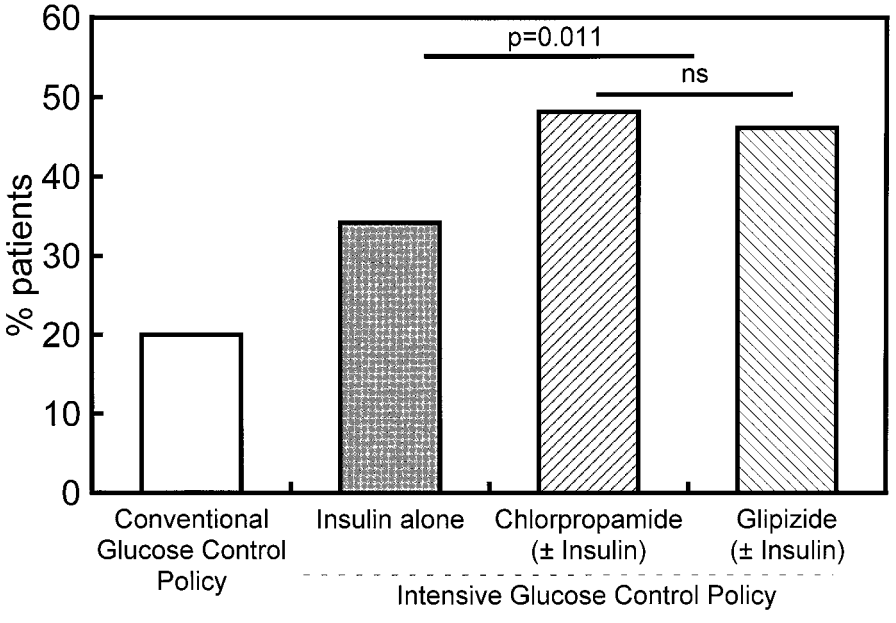

Figure 4—*Proportion (%) of patients achieving HbA_{1c} <7% at 6 years.*

APPENDIX

Participating centers

Torbay Hospital; Peterborough General Hospital; Scarborough Hospital; Derbyshire Royal Infirmary; Manchester Royal Infirmary; Hope Hospital, Salford; Leicester General Hospital; Royal Devon & Exeter Hospital.

References

1. UKPDS Group: Intensive blood glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). *Lancet* 352: 837–853, 1998
2. UKPDS Group: UK Prospective Diabetes Study 13: relative efficacy of randomly allocated diet, sulphonylurea, insulin, or metformin in patients with newly diagnosed non-insulin dependent diabetes followed for three years. *BMJ* 310:83–88, 1995
3. UKPDS Group: UK Prospective Diabetes Study 16: overview of six years' therapy of type 2 diabetes: a progressive disease. *Diabetes* 44:1249–1258, 1995
4. UKPDS Group: UK Prospective Diabetes Study 17: a nine-year update of a random-

ized, controlled trial on the effect of improved metabolic control on complications in non-insulin-dependent diabetes mellitus. *Ann Intern Med* 124:136–145, 1996
5. Turner RC, Holman RR, Matthews DR: Sulphonylurea failure and inadequacy: "non-insulin diabetes mellitus". In *Proceedings of the 13th IDF Conference, Hamilton Island, Australia, 26–28 1988.* Cameron D, Colagiuri S, Heding L, Kuhl C, Ma A, Mortimer R, Eds. Causeway Bay, Hong Kong, Excerpta Medica Asia, 1989.
6. UKPDS Group: UK Prospective Diabetes Study VIII: study design, progress and performance. *Diabetologia* 34:877–890, 1991
7. Johnson JL, Wolf SL, Kabadi UM: Efficacy of insulin and sulphonylurea combination therapy in type II diabetes: a meta-analysis of the randomised placebo-controlled trials. *Arch Intern Med* 156: 259–264, 1996
8. Holman RR, Turner RC: A practical guide to basal and prandial insulin therapy. *Diabetic Medicine* 5:45–53, 1985
9. UKPDS Group: UK Prospective Diabetes Study XI: biochemical risk factors in type 2 diabetic patients at diagnosis compared with age-matched normal subjects. *Diabet Med* 11:534–544, 1994
10. SAS Institute: *Statistical Analysis System*. 6th ed. Cary, NC, SAS Institute, 1990
11. Riddle MC, Schneider J: Beginning insulin treatment of obese patients with evening 70/30 insulin plus glimepiride versus insulin alone. *Diabetes Care* 21: 1052–1057, 1998
12. UKPDS Group: Association of glycaemia with macrovascular and microvascular complications of type 2 diabetes (UKPDS 35). *BMJ* 321:405–412, 2000
13. Holman RR, Steemson J, Turner RC: Sulphonylurea failure in type 2 diabetes: treatment with a basal insulin supplement. *Diabet Med* 4:457–462, 1987
14. Shank ML, Prato SD, DeFronzo RA: Bedtime insulin/daytime glipizide: effective therapy for sulfonylurea failures in MIDDM. *Diabetes* 44:165–172, 1995