

Combination Therapies With Insulin in Type 2 Diabetes

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The U.K. Prospective Diabetes Study (UKPDS) demonstrated that intensive glucose control with insulin or sulfonylureas markedly reduces the risk of microvascular complications (1). For myocardial infarction, the reduction in risk (16% for a 0.9% decrease in HbA_{1c}) was of borderline significance but corresponded closely to epidemiological predictions (14% decrease for a 1% drop in HbA_{1c}) (2). These data demonstrated that neither insulin nor sulfonylureas, despite causing hyperinsulinemia and weight gain, have adverse effects on cardiovascular outcome. Glycemic control deteriorated continuously, however, even in intensively treated patients in the UKPDS (1).

In the UKPDS, the worsening of glycemic control has been attributed to the natural course of type 2 diabetes and lack of efficacy of current antihyperglycemic therapies (1). Insulin therapy consisted of a single injection of ultralente or isophane insulin. If the daily dose exceeded 14 U, regular insulin was added and home-glucose monitoring was encouraged (1). Combination therapy regimens with insulin and oral agents were not used. We now know that 14 U of long-acting insulin is insufficient to control fasting glycemia in most type 2 diabetic patients (3). Since 1977, when the UKPDS was started, several studies have tried to define the optimal insulin treatment regimen for type 2 diabetic patients. These studies are the focus of this review and include studies comparing insulin alone to combination therapy with insulin and sulfonylureas (subject to meta-analyses in 1991 and 1992) (4,5) and more recent trials using metformin, glitazones, or acarbose in insulin combination therapy regimens. They do not contain data on cardiovascu-

lar end points but only on surrogate markers of risk of micro- and macrovascular complications, mostly data on glycemia, body weight, insulin doses, lipids, and in a few studies, also accurate data on the frequency of hypoglycemia.

According to a Medline search (1966–2000), insulin alone has been compared with insulin combination therapy in a total of 34 prospective studies that lasted at least 2 months and reported data on HbA_{1c} or HbA_{1c} in type 2 diabetic patients. Studies comparing glycemic control, weight gain, hypoglycemia, and insulin requirements between the two modes of treatment in insulin-naïve patients are listed in Table 1 and in previously insulin-treated patients are listed in Table 2. The studies have been ranked according to glycemic control at the end of the trial.

GLYCEMIC CONTROL AND INSULIN REQUIREMENTS

Insulin-naïve and previously insulin-treated patients.

In insulin-naïve patients in a total of 15 comparisons (10 studies), glycemic control was similar in most (11 of 15) comparisons and better with the insulin combination than the insulin-alone regimen in four comparisons (Table 1). In all studies, the daily insulin dose was lower with insulin combination therapy than with insulin alone. The weighted mean for the insulin-sparing effect of two drugs (sulfonylureas and metformin) in addition to insulin was 62%, i.e., 1.5–2.0 times that with regimens combining either metformin alone (–32%) or sulfonylureas alone (–42%) (Table 1) with insulin. These data imply that oral agents still have significant glucose-lowering effects even in

patients who are poorly controlled on oral drugs. One may also predict from these data that if the insulin dose is lowered less than ~30% when patients are transferred from insulin alone to insulin combined with sulfonylurea or metformin, glycemic control will be better during insulin combination therapy. This is documented by analysis of data from studies in previously insulin-treated patients (Table 2). In these comparisons, glycemic control was better in most (19 of 25) comparisons, but the insulin dose was decreased by only 19% in the combination regimens using metformin and by 21% in comparisons using insulin and sulfonylureas (Table 2). Thus, although in most comparisons (30 of 45) glycemic control has been better with insulin combination therapy regimens than with insulin alone, the difference may be at least partly explained by how the insulin dose has been decreased during insulin combination therapy. All glitazones have improved glycemic control when added to previous insulin treatment (Table 2). In a study directly comparing the insulin-sparing effects of troglitazone (600 mg/day) and metformin (1,700 mg/day), troglitazone had a greater (–53%) insulin-sparing effect than metformin (–31%). This was explained by insulin-sensitizing effects of troglitazone but not metformin (6).

WEIGHT GAIN

What determines weight gain during insulin therapy?

Although most patients with type 2 diabetes are overweight, weight loss precedes the diagnosis of type 2 diabetes (7). This weight loss is due to hyperglycemia-induced wasting of energy, as glucosuria and as energy used to overproduce glucose (8). When glucose control is improved with insulin and/or sulfonylureas, energy loss in the urine decreases or ceases, weight increases, and basal metabolic rate (kJ/min) (8–10) and dietary intake (11) remain unchanged. The increase in body weight increases basal metabolic rate, but this is counterbalanced by improved glycemic control, which decreases basal metabolic rate because less energy is

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Abbreviations: GADA, GAD antibodies; 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.

Table 1—Studies comparing combination treatment regimens with insulin to insulin alone in insulin-naïve type 2 diabetic patients

Reference no.	Combination regimen	Duration (months)	End HbA _{1c} *	Glycemia	Placebo control	Crossover/parallel	Weight gain	Hypoglycemia	Difference in insulin dose (%)†
Metformin alone									
12	MET + bedtime NPH	12	7.2% Comb	Better with MET‡	Yes	Parallel	Less with MET‡	No difference	-32
Metformin and sulfonylureas									
12	GLYB + MET + bedtime NPH	12	7.6% Comb	No difference	Yes	Parallel	No difference	No difference	-62
15	GLYB + MET + morning NPH	3	7.7% Comb	No difference	No	Parallel	No difference	No difference	-58
15	GLYB + MET + bedtime NPH	3	8.0% Comb	No difference	No	Parallel	Less with MET	No difference	-44
16	GLYB + MET + bedtime NPH	6	8.4% Ins	No difference	No	Parallel	Less with MET	No difference	-74
Weighted mean									
Sulfonylurea regimens									
25	GLIMEP + bedtime 30/70	6	7.6% Comb	No difference	Yes	Parallel	No difference	More with GLYB	-37
12	GLYB + bedtime NPH	12	7.8% Comb	No difference	Yes	Parallel	No difference	No difference	-55
29	GLYB + bedtime NPH	6	8.1% Comb	No difference	No	Parallel	No difference	No difference	-38
29	GLYB + morning NPH	6	8.2% Ins	No difference	No	Parallel	No difference	No difference	-33
55	GLYB + Ins	6	8.4% Comb	No difference	Yes	Parallel	No difference	ND	-43
32	GLYB + lispro t.i.d.	2	8.4% Comb	No difference	No	Parallel	No difference	No difference	-36
32	GLYB + bedtime NPH	2	8.5% Ins	No difference	No	Parallel	Less with GLYB	No difference	-56
28	GLYB + Ins	4	8.8% Comb	Better with GLYB	Yes	Crossover	No difference	—	-50
27	GLYB + Ins	4	9.8% Comb	Better with GLYB	Yes	Crossover	Less with Ins	—	-21
56	GLICL + Ins	12	11.8% Ins§	Better with GLICL	No	Parallel	—	—	-35
Weighted mean									

The trials are grouped according to the oral agent used and then ranked within these groups based on glycemic control at the end of treatment with the better regimen. Only trials lasting 2 months or longer are included; *HbA_{1c} at the end of treatment in the group with better control (even if not significantly better in one group versus the other); †% difference in insulin doses at the end of treatment with a combination regimen versus insulin alone; ‡significant difference; §HbA_{1c} Comb, combination regimen; GLICL, gliclazide; GLIMEP, glimepiride; GLYB, glyburide; Ins, regimen containing insulin alone; MET, metformin; 30/70 = an insulin mixture containing 30% regular insulin and 70% NPH.

needed for glucose overproduction. Because dietary intake remains unchanged (11), weight gain is proportional to reduction of glucosuria and can indeed be predicted based on fasting glucose concentrations (11). Because glucosuria appears when the fasting glucose concentration exceeds 10–12 mmol/l, weight gain is inevitable if insulin therapy is postponed until significant glucosuria occurs. In our experience, a 5-mmol/l (90-mg/dl) decrease in fasting glucose or a decrease in HbA_{1c} by 2.5% from a baseline of 15 mmol/l (270 mg/dl) is associated with a 5-kg weight gain during 1 year (or 2 kg/1% decrease in HbA_{1c}) (11). Thus, the main predictors of weight gain are initial glycemia and its response to treatment (11). The patient with poor glycemic control before initiation of insulin therapy but with a good treatment response is at greatest risk for weight gain.

Choice of oral agent and weight gain in insulin-naïve patients.

Only one trial has compared the combination of insulin with that of insulin and metformin alone in previously insulin-naïve patients (12). In this study, which lasted 12 months, the bedtime insulin-metformin regimen was superior to three other bedtime insulin regimens with respect to glycemic control, weight gain, and hypoglycemia (Table 1) (12). The ability of metformin to counteract weight gain and improve glycemia, when combined with insulin, has been confirmed in abstract reports (13,14). In these studies, weight gain was less despite comparable glycemia (13) or weight gain was similar despite better glycemic control (14) in patients using metformin and insulin compared with those using insulin and sulfonylureas or insulin alone. Data are heterogeneous regarding the ability of metformin to influence weight gain when combined with both insulin and sulfonylureas, compared with regimens containing insulin alone (Table 1). In two comparisons, weight gain was less with the combination regimen than with insulin alone (15,16), whereas two other comparisons revealed no difference (12,15) (Table 1, Fig. 1). The ability of metformin to counteract weight gain during insulin combination therapy has been attributed to a decrease in dietary intake (11).

Table 2—Studies comparing combination treatment regimens with insulin to insulin alone in previously insulin-treated type 2 diabetic patients

Reference no.	Combination regimen	Duration (months)	End HbA _{1c} * or HbA _{1c}	Placebo	Parallel/crossover	Glycemia	Weight gain	Hypoglycemia	Difference in insulin dose (%)†
Metformin regimens									
24	MET + insulin	6	6.5% Comb	Yes	Parallel	Better [‡] with MET	Less with MET [‡]	Less with MET [‡]	-23
42	MET + insulin	4	7.8% Comb	No	Parallel	Better with MET	Less with MET	—	-26
43	MET + insulin	3	7.8% Comb	Yes	Crossover	Better with MET	No difference	—	-3
57	MET + insulin	6	9.8% Comb	Yes	Parallel	Better with MET	ND	—	-20
	Weighted mean								-19
Sulfonylurea regimens									
45	GLYB + insulin	3	6.0% Comb	No	Crossover	No difference	No difference	—	-25
58	GLYB + insulin	3	7.0% Comb	Yes	Parallel	Better with GLYB	No difference	—	-20
46	SU + insulin	12	7.5% Comb	No	Parallel	No difference	No difference	—	-35
26	GLYB + insulin	4	8.3% Comb§	Yes	Crossover	Better with GLYB	No difference	More with GLY	-20
47	TOLAZ + insulin	3	8.8% Comb§	Yes	Crossover	Better with GLYB	Fixed	—	-23
59	GLYB + insulin	12	8.8% Comb§	Yes	Parallel	Better with GLYB	—	—	-47
60	GLYB + insulin	3	9.1% Comb	Yes	Crossover	Better with GLYB	—	—	-7
61	GLYB + insulin	4	9.6% Comb	Yes	Parallel	Better with GLYB	—	—	Fixed
62	GLIP + insulin	3	9.8% Comb§	Yes	Crossover	No difference	—	—	-35
49	GLYB + insulin	4	10.2 Comb§	Yes	Crossover	Better with GLYB	No difference	—	-3
48	GLYB + insulin	11	10.3% Ins§	Yes	Crossover	Better with GLYB	No difference	—	-7
50	GLYB insulin	2	11.0% Comb§	Yes	Crossover	No difference	No difference	—	-2
44	GLYB + insulin	2	12.4% Comb§	Yes	Crossover	Better with GLYB	—	—	Fixed
63	TOLAZ + insulin	2	12.6% Comb§	Yes	Crossover	No difference	—	—	Fixed
64	GLYB + insulin	12	12.9% Ins	Yes	Crossover	No difference	No difference	—	-22
51	GLYB + insulin	2	13.0% Comb§	Yes	Crossover	Better with GLYB	No difference	—	±0
	Weighted mean								-21
Glitazone									
54	ROSI + insulin	6	7.8%	Yes	Parallel	Better with ROSI	More with ROSI	More with ROSI	±0
52	TRO + insulin	6	7.9%	Yes	Parallel	Better with TRO	More with TRO	More with TRO	-46
53	PIO + insulin	4	8.6%	Yes	Parallel	Better with PIO	More with PIO	More with PIO	—
α-Glucosidase inhibitor									
65	ACARB + insulin	6	8.3%	Yes	Parallel	Better with ACARB	—	No difference	Fixed
66	ACARB + insulin	12	7.3%	Yes	Parallel	Better with ACARB	No difference	No difference	—

The trials are grouped according to the oral agent used and then ranked within these groups based on glycemic control at the end of treatment with the better regimen. Only trials lasting 2 months or longer are included. *HbA_{1c} at the end of treatment in the group with better control (even if not significantly better in one group versus the other); †% difference in insulin doses at the end of treatment with a combination regimen versus insulin alone; ‡statistically significant difference between insulin combination therapy versus insulin alone; §HbA_{1c} reference range higher than that for HbA_{1c}; ||trials in which the insulin dose was fixed are not included in the calculation of the weighted mean. ACARB, acarbose; Comb, combination regimen; GLIP, glipizide; Ins, regimen containing insulin; PIO, pioglitazone; ROSI, rosiglitazone; SU, various sulfonylureas; TOLAZ, tolazamide; TRO, troglitazone.

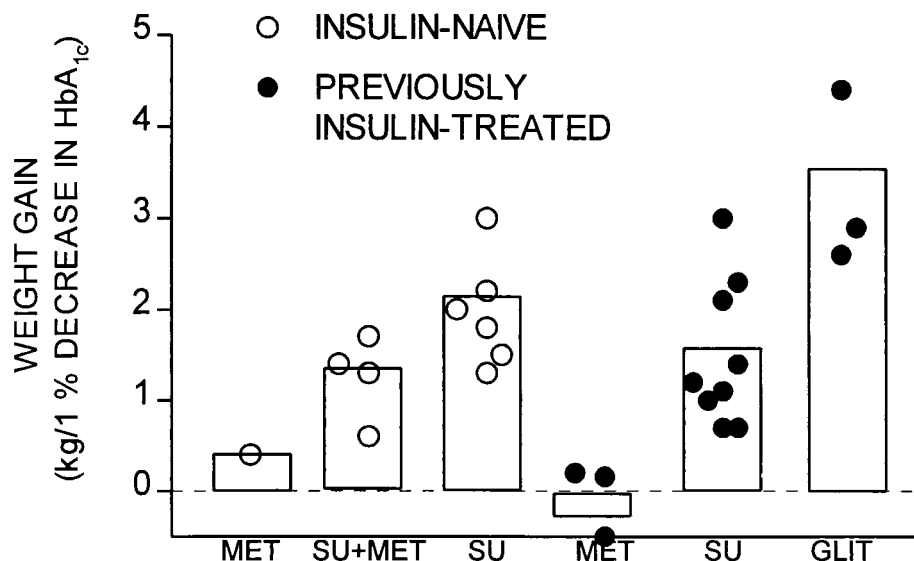


Figure 1—Weight gain in previously insulin-treated patients during treatment with insulin combination regimens containing metformin (MET) (24,42,43), various sulfonylureas (SU) (26,44–51), and glitazones (GLIT) (52–54) and in insulin-naïve patients treated with insulin and MET (12), SU+MET (12,15,16), and SU (12,25,27–29).

Choice of oral agent and weight gain in previously insulin-treated patients.

Switching patients from treatment with insulin alone to insulin combination therapy with metformin has been associated with less weight gain in two of three studies, whereas no difference was found in any of the 16 comparisons in which insulin plus sulfonylurea was compared with insulin alone, despite better control in 10 of 16 comparisons (Table 2). It is unclear whether this is because weight was not accurately recorded or because the larger dose of exogenous insulin or the greater number of insulin injections used in insulin alone as compared with the insulin combination regimen had independent weight-promoting effects. In studies comparing insulin-glitazone treatment with insulin alone, glycemic control was better in each study with the insulin-glitazone combination than with insulin alone. Better glycemic control was also associated with greater weight gain in each of the three studies. Although the amount of weight gain relative to the improvement in glycemic control seemed slightly greater than with sulfonylureas (Fig. 1), data on insulin-glitazone combination therapy are still sparse. The significance of weight gain with glitazones is also difficult to judge, because glitazones may be beneficial in redistributing fat from visceral to sub-

cutaneous sites (17–19). A small fraction of weight gain with glitazones could be due to peripheral edema (20,21).

HYPOGLYCEMIAS

Frequency of hypoglycemia in type 1 versus type 2 diabetes.

In both patients with type 1 (22) and type 2 (12) diabetes, the frequency of hypoglycemia is inversely proportional to glycemic control. In the Diabetes Control and Complications Trial, in patients with HbA_{1c} between 7 and 8%, the frequency of severe hypoglycemia requiring assistance in the provision of treatment was 0.62 per patient per year (22). In contrast, in the FINFAT study (12), the Kumamoto study (23), or other studies of type 2 diabetes in which comparable glycemic control was achieved (24,25), there were no severe hypoglycemia. The frequency of biochemical hypoglycemia (blood glucose <3.5 mmol/l) was 1.9 per patient per year in patients treated with insulin plus metformin and approximately twice as high in the other groups in the FINFAT study (12). In the latter study, HbA_{1c} averaged between 7 and 8% in all groups for 1 year. These data, although derived from separate studies, suggest that hypoglycemia is much less of a problem in type 2 diabetic patients than in type 1 diabetic patients.

Does the oral agent influence the occurrence of hypoglycemia independent of glycemic control?

The occurrence of hypoglycemia has been sparsely reported [eight comparisons in insulin-naïve patients (Table 1) and five comparisons in previously insulin-treated patients (Table 2)]. In insulin-naïve patients, use of insulin combination therapy with metformin has been associated with less hypoglycemia than with insulin alone, despite better glycemic control with the insulin-combination regimen (12). No difference was observed between insulin-alone and insulin-sulfonylurea regimens in five of seven studies; in two studies (25,26), there were more cases of hypoglycemia with insulin and sulfonylurea than with insulin alone (Tables 1 and 2). No difference in the incidence of hypoglycemia was observed between insulin alone compared with insulin plus sulfonylurea and metformin regimens (Tables 1 and 2). In the latter studies, there was also no difference in glycemic control. In all three studies comparing insulin-glitazone combination therapy to insulin alone, the frequency of hypoglycemia was higher and glycemic control was better with the insulin-combination regimen. These data suggest that with the possible exception of metformin, use of insulin combination therapy is accompanied by a similar frequency of hypoglycemia than is use of insulin alone.

CHANGES IN SERUM TRIGLYCERIDES AND OTHER LIPIDS AND LIPOPROTEINS

Insulin-naïve patients.

Data on changes in serum triglycerides and glycemia in insulin-naïve patients are summarized in Table 3. As judged from the weighted means of insulin-alone regimens, a decrease in HbA_{1c} from ~10 to 8% (i.e., by 2%) is associated with a 0.7- to 0.8-mmol/l decrease in serum triglycerides from an initial concentration of 2.4–2.7 mmol/l. With insulin combination therapy regimens, a decrease of HbA_{1c} by 2% decreases serum triglycerides by 0.4–0.6 mmol/l (Table 3). In all except one study, insulin alone lowered serum triglycerides slightly more than insulin combination therapy, although there was no significant difference in the lowering of serum triglycerides with the two modes of therapy in any of the studies

Table 3—Changes in glycosylated hemoglobin and serum triglycerides during treatment with insulin alone as compared with combination therapies with insulin and oral agents in insulin-naïve patients

Ref. no.	Combination regimen	Duration (months)	Baseline	Change	Baseline	Change	Baseline	Change	Baseline	Change	Better†	Better†
			HbA _{1c} Ins	in HbA _{1c} Ins	HbA _{1c} Comb	in HbA _{1c} Comb	S-Tg Ins	in S-Tg Ins	S-Tg Comb	in S-Tg Comb	regimen S-Tg	regimen glycemia
Metformin alone												
12	MET + bedtime NPH	12	9.9	-2.0‡	9.8	-2.5‡	2.6	-0.9‡	2.4	-0.7‡	NS	Comb
Metformin and sulfonylureas												
12	GLYB + MET + bedtime NPH	12	9.9	-2.0‡	9.9	-2.1‡	2.6	-0.9‡	2.3	-0.4‡	NS	NS
15	GLYB + MET + morning NPH	3	9.6	-1.6‡	9.5	-1.7‡	2.4	-0.6‡	2.6	-0.3	NS	NS
15	GLYB + MET + bedtime NPH	3	9.6	-1.6‡	9.9	-1.9‡	2.4	-0.6‡	2.5	-0.6‡	NS	NS
16	GLYB ± MET + bedtime NPH	6	10.7	-2.3‡	10.2	-1.5‡	1.8	-0.4‡	2.1	-0.2	NS	NS
Weighted mean			9.9	-1.9	9.9	-1.9	2.4	-0.7	2.4	-0.4		
Sulfonylurea regimens												
25	GLIMEP + bedtime 30/70	6	9.9	-2.0‡	9.7	-2.1‡	3.1	-1.0‡	3.2	-0.3‡	NS	NS
12	GLYB + bedtime NPH	12	9.9	-2.0‡	9.8	-2.0‡	2.6	-0.8‡	2.7	-0.8‡	NS	NS
29	GLYB + bedtime NPH	6	11.2	-3.0‡	10.5	-2.3‡	2.4	-0.7‡	2.0	-0.3‡	NS	NS
29	GLYB + morning NPH	6	11.2	-3.0‡	11.1	-2.6‡	2.4	-0.7‡	2.2	-0.3	NS	NS
55	GLYB + insulin	6	11.5*	-2.2‡	10.4*	-2.2‡	2.0	-0.4	2.2	-0.3	NS	NS
28	GLYB + insulin	4	9.7*	-0.8	10.1*	-1.3	3.1	-0.6	2.8	-0.8‡	Comb	Comb
27	GLYB + insulin	4	10.4*	0.2	10.6*	-0.8‡	3.6	-1.1‡	3.6	-1.2‡	NS	Comb
Weighted mean			10.5	-2.2	10.2	-2.1	2.7	-0.8	2.7	-0.6		

The trials are grouped according to the oral agent used and then ranked within these groups based on glycemic control at the end of treatment with the better regimen. Only trials lasting at least 2 months are included. *HbA_{1c} value; †denotes a statistically significant difference between insulin combination therapy versus insulin alone; ‡significant difference at the end versus start of the treatment period. Comb, combination regimen; Ins, regimen containing insulin alone; S-Tg, serum triglycerides (mmol/l). For other abbreviations, see Table 1.

(Table 3). LDL and HDL cholesterol concentrations remained unchanged in all studies, with no differences between regimens (12,15,16,25,27–29).

Previously insulin-treated patients.

As summarized in Table 4, the greater improvement in glycemic control with insulin combination therapy than with insulin alone in 11 of 14 studies has not been consistently (4 of 11 studies) associated with a greater decrease in serum triglycerides. These data demonstrate that factors other than average glucose concentrations determine the degree of lowering of serum triglycerides. Overall, the available comparisons of changes in serum lipid and lipoprotein concentrations in both insulin-naïve and previously insulin-treated patients do not allow definitive conclusions and do not support choice of one treatment regimen over another.

BLOOD PRESSURE

Regarding blood pressure, in a follow-up study of the patients participating in the FINMIS study (15,30), blood pressure increased significantly in the entire group of 100 patients during 1 year. Weight gain correlated both with the increase in blood pressure and with an increase in the LDL

cholesterol concentrations (30). Three shorter studies reported data on blood pressure (15,25,27) but found no changes in blood pressure or differences between regimens.

SPECIAL QUESTIONS

Choice of insulin regimen during insulin combination therapy: NPH insulin or insulin glargine?

Regarding basal insulinization, the commonly used intermediate-acting insulin (NPH) is not ideal for once-daily use. In the FINMIS study, in patients with type 2 diabetes with a mean BMI of 29 kg/m², injection of NPH insulin at 9:00 P.M. resulted in maximal glucose lowering between 4:00 and 8:00 A.M., but the effect was gone by 3:00 P.M., i.e., 18 h after the injection, and dinnertime glucose concentrations were unnecessarily high. The recently approved long-acting insulin analog insulin glargine seems to overcome these problems. In a study comparing NPH plus oral agents to insulin glargine plus oral agents in 423 insulin-naïve type 2 diabetic patients for 1 year, all hypoglycemia were 35% lower and nocturnal hypoglycemia were 56% lower with insulin glargine than with NPH (Fig. 2). Dinner-

time glucose levels were also significantly lower with insulin glargine than with NPH (Fig. 2).

Regular insulin or short-acting insulin analogs compared with NPH during combination therapy.

Regular insulin three times per day plus a sulfonylurea has been compared with a single injection of NPH taken at bedtime and a sulfonylurea. No difference in glycemic control was found, but weight gain was significantly greater with three injections of regular insulin than with a single injection of bedtime NPH insulin (31). Greater weight gain with no difference in glycemic control has also been reported with three injections of lispro plus sulfonylurea compared with NPH plus sulfonylurea (32) (Table 5).

Timing of the intermediate-acting insulin injection.

The pros and cons of timing of the intermediate-acting insulin injection has been examined in three studies (15,33,34). In two studies, a bedtime injection was recommended because it resulted in less weight gain (15) or less hypoglycemia (34) than a morning injection. In the third

Table 4—Changes in glycosylated hemoglobin and serum triglycerides during treatment with insulin alone as compared with insulin combination therapy in previously insulin-treated patients

Ref. no.	Combination regimen	Duration (months)	Baseline HbA _{1c} Ins	Change in HbA _{1c} Ins	Baseline HbA _{1c} Comb	Change in HbA _{1c} Comb	Baseline S-Tg Ins	Change in S-Tg Ins	Baseline S-Tg Comb	Change in S-Tg Comb	Better† regimen S-Tg	Better† regimen glycemia
Metformin												
24	MET + insulin	6	9	-1.6§	9.1	-2.5§	2.5	-0.4	2.3	-0.1	NS	Comb
42	MET + insulin	4	9.6	0.0	9.6	-1.9§	2.4	-0.1	2.0	-0.4§	Comb	Comb
43	MET + insulin	6	11.5	-0.2	11.7	-1.9	2.8	-0.0	2.9	-0.3§	Comb	Comb
57	MET + insulin	3	8.9	-0.5§	8.9	-1.1§	2.2	-1.0§	2.2	-0.9§	NS	Comb
	Weighted mean		9.8	-0.6	10.0	-1.9	2.5	-0.4	2.4	-0.4		
Sulfonylurea												
45	GLYB + insulin	3	6.7	-0.4	6.3	-0.3	1.5	-0.08	1.5	0.2	NS	NS
46	SU + insulin	12	10.2	-2.4§	9.8	-2.3§	2.3	-0.6	2.5	-0.8	NS	NS
26	GLYB + insulin	4	9.2*	-0.1	9.2*	-0.9§	1.2	0.1	1.2	0.1§	Ins	Comb
47	TOLAZ + insulin	3	10.7*	-1.5§	10.7*	-1.9	2.1	0.0	2.1	-0.5§	Comb	Comb
48	GLYB + insulin	11	10.3	-1.3§	11.1	-2.0§	1.7	0.1	2.4	-0.7	NS	NS
61	GLYB + insulin	4	10.4	0.0	10.9	-1.3§	1.4	-0.1	1.8	-0.1	NS	Comb
51	GLYB + insulin	2	14.0*	-0.6	14.0*	-1.0	2.1	-0.4	2.1	-0.2	NS	Comb
	Weighted mean		10.1	-1.0	10.1	-1.4	1.8	-0.1	2.0	-0.2		
Glitazones												
52	TRO + insulin	6	8.9	0.1	9.0	-1.2	2.6	-0.5	2.5	-0.1	NS	Comb
54	ROSI + insulin	6	9.4	-0.1	9.3	-0.4	3.0	-0.3	2.7	-0.4	NS	Comb
	Weighted mean		9.2	-0.0	9.2	-1.3	2.8	0.1	2.6	-0.2		
α-Glucosidase inhibitor												
65	ACARB + insulin	6	8.7	0.1	8.8	-0.6§	2.1†	—	2.2‡	—	Comb	Comb

The trials are grouped as in Table 3. Only trials lasting at least 2 months are included. *HbA_{1c}; †statistically significant difference between insulin combination therapy versus insulin alone; ‡serum triglycerides 120 min after a standardized meal challenge; §significant difference at the end versus start of the treatment period. There were no significant differences between changes in serum triglycerides with insulin alone versus insulin combination therapy. Abbreviations as in Tables 2 and 3.

study, no differences in glycemia or weight gain were found (33).

PREDICTION OF INSULIN REQUIREMENTS

Variation in hepatic insulin sensitivity seems to be much more important than insulin absorption in determining insulin requirements during combination therapy with NPH insulin (3). Hepatic insulin sensitivity cannot be routinely measured but correlates with various indexes of obesity (3). In type 2 diabetic patients with a mean BMI of 29 kg/m², to achieve an average HbA_{1c} of ~7.5% from a baseline value of 10%, the mean bedtime NPH insulin dose for body weights of 70, 80, 90, and 100 kg has been 0.2, 0.3, 0.4, and 0.5 IU/kg (3,11). However, interindividual variation is large and has varied 20-fold between 8 and 168 IU per day (12), which implies that these average predictions are not accurate enough to be used on an individual level.

Autoantibodies to glutamic acid de-

carboxylase (GADA) predict an increased likelihood of insulin requirement in both young and old adults with type 2 diabetes (35). In 3,672 newly diagnosed patients in the UKPDS, 34% of those aged 25–34 years and 7% of those aged 55–65 years had GADA (35). Among patients older than 55 years at diagnosis, 34% of those with GADA and 5% with autoantibodies to neither GADA nor islet cell cytoplasm required insulin therapy. In these older patients, only the presence of GADA but not phenotypic features such as BMI predicted insulin requirement. There are no studies comparing insulin combination regimens with insulin alone in these patients, who are often classified as having type 2 diabetes but actually have type 1 diabetes (36). In patients in whom signs of absolute insulin deficiency (rapid weight loss, ketonuria) ultimately develop, the presence of GADA may guide the choice of a basal-bolus-type full insulin-replacement regimen (37).

PREDICTORS OF A GLYCEMIC RESPONSE TO INSULIN COMBINATION THERAPY

In studies in which the insulin dose is titrated aggressively to reach glycemic targets, the decrease in HbA_{1c} will be directly proportional to its initial level. Of other factors, obesity predicts a poor response to any type of insulin therapy, especially if insufficient doses of insulin are used (30,38). In addition, and as discussed above, GADA may predict poor response to combination therapy.

PRACTICAL ALGORITHM TO INITIATE INSULIN THERAPY

Initiation of insulin therapy on an ambulatory basis in type 2 diabetic patients has been shown to be as safe and effective as an inpatient program (39). Regardless of the insulin treatment regimen chosen, the insulin dose should be adjusted to reach glycemic targets. Considering the large interindividual variation in insulin re-

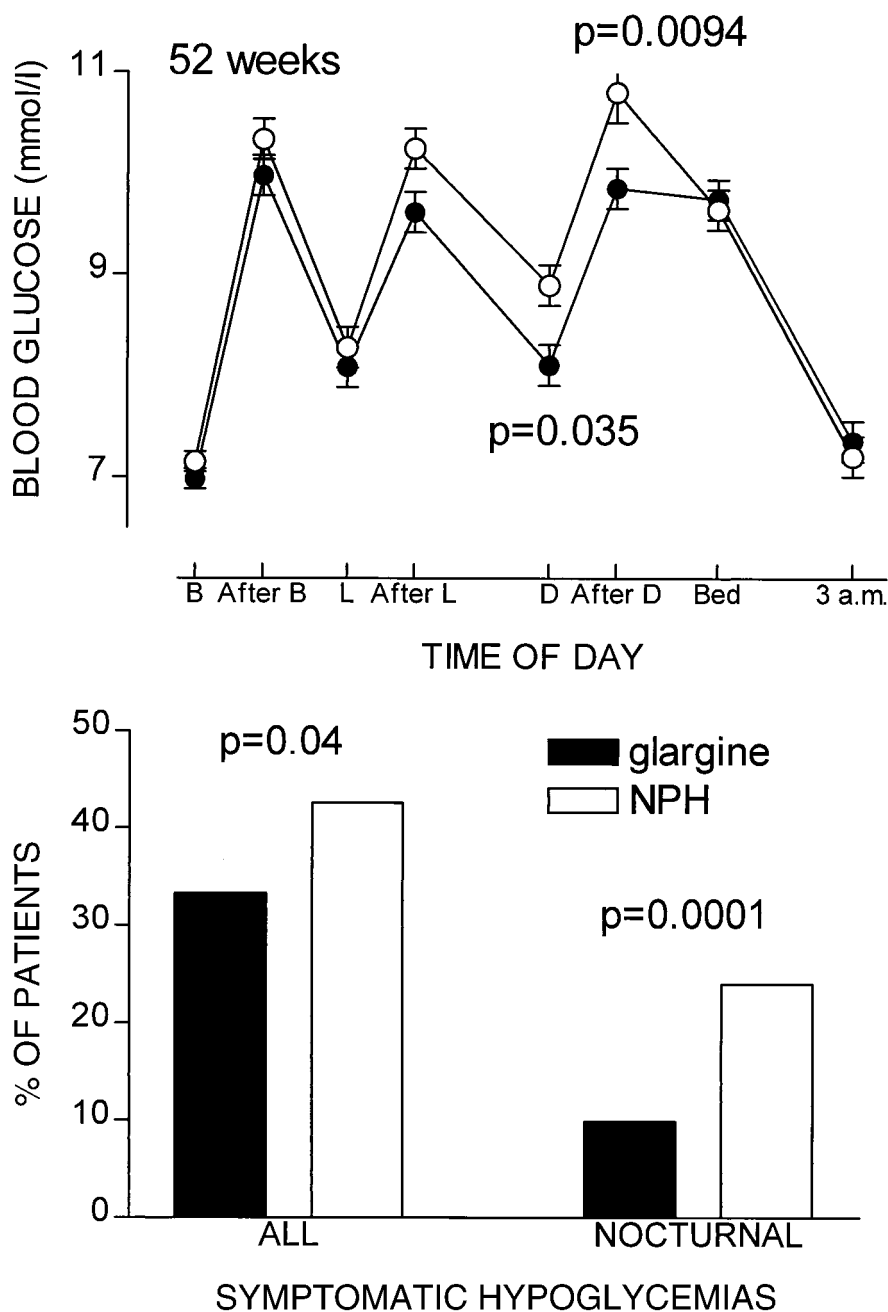


Figure 2—Upper panel: Diurnal glucose profiles after 52 weeks of treatment of 423 patients using oral hypoglycemic agents with either insulin glargine (●) or NPH (○). Lower panel: The percentage of patients experiencing any symptomatic hypoglycemia (ALL) or nocturnal hypoglycemia (NOCTURNAL) in the same study (40).

quirements, it is difficult to define the correct insulin dose by performing dose adjustments only at outpatient visits, unless these are very frequent. In our experience of treating insulin-naïve patients (12,15), the best method of defining the insulin dose is teaching the patient to self-adjust the dose based on results of home glucose monitoring. This is easiest to perform if the dose adjustment is based on

measurement of fasting plasma glucose only. Fasting plasma glucose is not influenced by size, composition, or rate of absorption of meals as much as by postprandial glucose levels, and its measurement does not interfere with daily activities. The maximal action of NPH given at bedtime is exerted on fasting glucose, which, therefore, is a particularly suitable target for titration of the dose when insu-

lin combination therapy with NPH or insulin glargine is used. However, because especially NPH insulin is unable to adequately control postdinner glycemia, fasting glucose must be in the normal range (4–6 mmol/l) for average glycemic control, measured using HbA_{1c} to be <7.5%. A simple method of initiating insulin therapy, developed based on experience from the FINFAT study, is shown in Table 5 (12). The patient is assumed to be insulin-naïve and on maximal doses of sulfonylureas and metformin. The recommendation to discontinue the sulfonylurea (glyburide) but not metformin after insulin combination therapy is started is based on the inability of some patients to adequately titrate the dose of bedtime NPH because of hypoglycemia (12). An increase in mild hypoglycemia was also reported by Riddle and Schneider (25) with glimepiride combined with a single injection of 30/70 insulin at 6:00 P.M. compared with two injections of 30/70 insulin. Hypoglycemia may not be a problem with peakless insulins such as insulin glargine (40). Discontinuation of sulfonylurea when insulin therapy is started may retard achievement of good glycemic control unless the insulin dose is rapidly increased (12,25). Glitazones could be an additional or alternative component in the oral hypoglycemic agent regimen, but there are no studies in insulin-naïve patients.

CONCLUDING REMARKS

Against the emerging epidemic of type 2 diabetes, studies comparing different insulin treatment regimens are sparse and include only a small number of patients treated for a maximum of 1 year (Tables 1 and 2). Data on effects of insulin-combination therapy versus insulin alone on diabetic microvascular and macrovascular complications are nonexistent. The main reason for the paucity of data may be the reluctance of private funding agencies to support studies using pharmacological agents and the reluctance of industry to support studies with established preparations. The development of new agents such as glitazones and insulin analogs have increased the number of patients included in various trials, but many company-initiated trials are designed to fulfill licensing requirements and must be performed in multiple centers to save time. Although some company-initiated trials are of superb quality, others suffer from inadequate glycemic control and may lack the comparisons the

Table 5—Studies comparing insulin combination regimens with different insulin injection regimens in type 2 diabetic patients (oral agents similar in all regimens)

Reference no.	Regimen 1	n	Regimen 2	n	Glycemia	Weight gain	Hypoglycemia
40	Bedtime NPH + OHA*	208	Bedtime glargine + OHA*	214	No difference	No difference	Less with glargine†
15	Bedtime NPH + MET + SU	28	Morning NPH + MET + SU	32	No difference	Less† with bedtime NPH	No difference
34	Bedtime NPH + SU	15	Morning NPH + SU	14	No difference	No difference	Less with bedtime NPH
33	Bedtime NPH + SU	24	Morning NPH + SU	24	No difference	No difference	No difference
31	Bedtime NPH + SU	39	3 × regular + SU	41	No difference	Less with bedtime NPH	No difference
32	Bedtime NPH + SU	135	3 × lispro + SU	139	No difference	Less with bedtime NPH	No difference

*OHA, oral hypoglycemic agents, 59% SU + MET, no differences in OHA between groups using NPH versus insulin glargine; †statistically significant difference between regimen 1 and regimen 2.

clinicians would be interested in. Despite these deficiencies, some conclusions regarding the role of insulin combination therapy in the treatment of type 2 diabetic patients seem justified.

No study reported worse glycemic control with insulin combination therapy than with insulin alone. Glycemic control was better with insulin combination therapy than with insulin alone in most studies of previously insulin-treated patients, but this could be explained by a smaller difference (~20% for metformin or sulfonylureas) (Table 2) in the insulin dose between the two modes of treatment than in

studies performed in insulin-naïve patients (30–40%, Table 1). Combination regimens allow use of less insulin injections, which may ease titration of the insulin dose and compliance (12,15,41). These benefits must be balanced against the side effects of oral drugs and, in some countries, their cost. Abnormal renal or liver function also limits the use of many oral agents. Weight gain seems proportional to the number of insulin injections used (12,15,31,32) and can be counteracted by inclusion of metformin in the treatment regimen. Metformin also seems to reduce the incidence of hypoglycemia

(12), as does the use of the peakless long-acting insulin analog insulin glargine compared with NPH (40). These considerations and the need to treat not only hyperglycemia but also other risk factors in type 2 diabetes support the use of simple insulin combination regimens such as insulin glargine and metformin and or a sulfonylurea (40). The prevailing view that patients who are poorly responsive to such a regimen benefit from adding additional insulin injections is not supported by existing data. Instead, special emphasis should be placed on increasing the dose of the single long-acting insulin to a

Table 6—Simple algorithm to start insulin combination therapy in an insulin-naïve patient treated with oral combination therapy

Objectives	Details
Visit–1, before start of insulin therapy	
<ul style="list-style-type: none"> Teach home-glucose monitoring Correct gross errors in diet 	Home glucose monitoring <ul style="list-style-type: none"> Measure fasting glucose daily during first weeks or months; after reaching target frequency can be even once a week
Visit 0, initiation of insulin therapy	
<ul style="list-style-type: none"> Stop sulfonylurea, continue metformin 2 g/day† Teach insulin injection technique Define initial dose of insulin (glargine, NPH or 30/70 at 6:00 P.M. or later) Give written instructions regarding self-adjustment of the insulin dose Teach symptoms of hypoglycemia Schedule a phone call after 1 week and visit after 2–4 weeks 	Initial dose of insulin (insulin glargine, NPH, or ultralente) <ul style="list-style-type: none"> Irrelevant if adjusted by patient Safe starting dose = fasting glucose (mmol/l). i.e., 10 IU if fasting glucose is 10 mmol/l Self-adjustment of insulin doses <ul style="list-style-type: none"> If fasting glucose exceeds 5.5 mmol/l (100 mg/dl) on three consecutive measurements, increase bedtime insulin dose by 2 IU During combination therapy with NPH and oral agents (ref. FINFAT), or fasting glucose of ≤6 mmol/l corresponds to ≤7.5% HbA_{1c}
Subsequent visits	
<ul style="list-style-type: none"> Individualize frequency—consider electronic transfer of home glucose-monitoring Results and phone calls instead of outpatient visits 	

*There are no data on use of glitazones in combination therapy with insulin in insulin-naïve patients; †based on the FINFAT study, in which glyburide and NPH insulin were used and use of this combination prevented adequate titration of the insulin dose (12); a higher incidence of symptoms of mild hypoglycemia was found using glimepiride combined with 30/70 insulin given at 6:00 P.M. Similar problems were not reported in another study in which glimepiride was combined with 30–70 insulin at 6:00 P.M. (25) and may not be a problem with insulin glargine (40). Note that stopping a sulfonylurea necessitates a rapid increase in the insulin dose, which can be performed by teaching the patient self-adjustment of the insulin dose.

dose that normalizes the fasting glucose concentration.

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