Comparison of Basal Insulin Added to Oral Agents Versus Twice-Daily Premixed Insulin as Initial Insulin Therapy for Type 2 Diabetes

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OBJECTIVE — To compare the efficacy and safety of adding once-daily basal insulin versus switching to twice-daily premixed insulin in type 2 diabetic patients insufficiently controlled by oral antidiabetic agents (OADs).

RESEARCH DESIGN AND METHODS — In a 24-week, multinational, multicenter, open, parallel group clinical trial, 371 insulin-naïve patients with poor glycemic control (fasting blood glucose [FBG] ≥120 mg/dl, HbA_{1c} 7.5–10.5%) on OADs (sulfonylurea plus metformin) were randomized to once-daily morning insulin glargine plus glimepiride and metformin (glargine plus OAD) or to 30% regular/70% human NPH insulin (70/30) twice daily without OADs. Insulin dosage was titrated to target FBG ≤100 mg/dl (both insulins) and predinner blood glucose ≤100 mg/dl (70/30 only) using a weekly forced-titration algorithm.

RESULTS — Mean HbA_{1c} decrease from baseline was significantly more pronounced (−1.64 vs. −1.31%, $P = 0.0003$), and more patients reached HbA_{1c} ≤7.0% without confirmed nocturnal hypoglycemia (45.5 vs. 28.6%, $P = 0.0013$) with glargine plus OAD than with 70/30. Similarly, FBG decrease was greater with glargine plus OAD (adjusted mean difference −17 mg/dl [−0.9 mmol/l], $P < 0.0001$), and more patients reached target FBG ≤100 mg/dl with glargine plus OAD than with 70/30 (31.6 vs. 15.0%, $P = 0.0001$). Glargine plus OAD patients had fewer confirmed hypoglycemic episodes than 70/30 patients (mean 4.07 vs. 9.87/patient-year, $P < 0.0001$).

CONCLUSIONS — Initiating insulin treatment by adding basal insulin glargine once daily to glimepiride plus metformin treatment was safer and more effective than beginning twice-daily injections of 70/30 and discontinuing OADs in type 2 diabetic patients inadequately controlled with OADs.

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The association between poor glycemic control and the occurrence of micro- and macrovascular complications has been demonstrated in patients with type 1 and type 2 diabetes (1–3); however, achieving glycemic control, preferably with HbA_{1c} values <7%, can markedly reduce the risk of such complications (4) and is now recommended clinical practice (5,6). In many patients, insulin treatment is required to achieve good glycemic control (1).

Consensus opinion on how or when to initiate insulin treatment in type 2 diabetic patients is lacking, and treatment regimens are known to vary between countries. Since most patients with type 2 diabetes are older and physicians' time is limited, the insulin regimen should be easy to apply. However, few studies have directly compared the leading methods. We studied two commonly used, simple regimens for initiating insulin therapy. One approach consists of stopping oral antidiabetic agent (OAD) therapy and initiating two injections of insulin, often premixed insulin containing a fixed ratio of regular and intermediate-acting insulin (NPH), administered twice daily. The European Diabetes Policy Group (5) recommended that, in the majority of patients with type 2 diabetes, insulin therapy should be initiated using premixed insulin twice daily. Nearly 40% of insulin-treated patients with diabetes worldwide are treated with premixed insulin (7). Indeed, a German study has reported that premixed insulin constitutes the majority (>80%) of insulin usage in patients with type 1 and type 2 diabetes (8). Another approach includes the use of a basal insulin with continued OADs. The present study compared the effectiveness of switching from OADs to twice-daily premixed human 70/30 insulin versus adding a once-daily injection of basal insulin glargine to prior OADs. The method chosen is, similar to twice-daily premixed insulin, a simple one: insulin glargine has a 24-h time-action profile with no pronounced peak (9,10) and can therefore be administered once daily, while glimepiride can be taken once daily and metformin as previously.

RESEARCH DESIGN AND METHODS

— Male or female patients aged 35–75 years with a type 2 diabetes duration of at least 1 year and treated with

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Abbreviations: FBG, fasting blood glucose; OAD, oral antidiabetic agent.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

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a stable dose of sulfonylurea and metformin for at least 1 month were enrolled at 66 sites in 10 European countries. Further inclusion criteria included BMI ≤35 kg/m^2, HbA_{1c} levels between 7.5 and 10.5%, and fasting blood glucose (FBG) levels ≥120 mg/dl (≥6.7 mmol/l). Exclusion criteria included any additional use of other oral blood glucose–lowering agents, prior use of insulin exceeding 3 days, and a history of ketoacidosis. The study was conducted in accordance with the Declaration of Helsinki. Approval by institutional ethics committees was obtained for each participating site. All patients provided written informed consent before study entry.

This was a parallel group, open-label, randomized, multinational clinical trial with a 1- to 4-week screening phase and a 24-week treatment phase. A 1:1 randomization schedule stratified by center sequentially assigned treatment codes to eligible patients, using a central randomization service of the electronic case report form InForm (Phaseforward, Maidenhead, U.K.).

Previous sulfonylurea therapies were replaced with 3 or 4 mg glimepiride (Amaryl; Aventis Pharma) during the screening phase. Metformin (≥850 mg; Metformin Basics; Basics) during the study was provided and taken at the same dose as before study entry. The dosage of both agents remained unchanged throughout the study. At the baseline visit, patients were randomly assigned to either insulin glargine (Lantus; Aventis Pharma) given once daily in the morning in combination with glimepiride and metformin (glargine plus OAD) or to human premixed insulin (30% regular, 70% NPH insulin; Insulin Actraphane HM 30/70; Novo Nordisk) to be administered twice daily (before breakfast and dinner), while glimepiride and metformin were discontinued (70/30). The insulins were injected using Optipen 1E for insulin glargine and NovoPen for premixed insulin. The starting dose for insulin glargine was 10 IU in the morning and, for premixed insulin, 10 IU before breakfast and 10 IU before dinner. These starting doses could be lowered if considered clinically necessary by the investigator. Insulin doses were adjusted by a forced titration regimen calling for weekly adjustments for 8 weeks and at 2-week intervals thereafter for both groups, according to daily self-monitored capillary whole blood glucose measurements using meters (AccuChek Sensor; Roche Diagnostics). For both groups, the FBG target was 100 mg/dl (5.6 mmol/l), and the before dinner blood glucose target for the 70/30 group was 100 mg/dl (5.6 mmol/l), with a stepwise increase of insulin depending on the blood glucose values as follows: blood glucose >100–120 mg/dl, increased by 2 IU/day; blood glucose >120–140 mg/dl, increased by 4 IU/day; blood glucose >140–160 mg/dl, increased by 6 IU/day; and blood glucose >160 mg/dl, increased by 8 IU/day, unless symptoms of hypoglycemia occurred. Hypoglycemia was confirmed by blood glucose <60 mg/dl. Severe hypoglycemia was defined as an event with symptoms consistent with hypoglycemia during which the person required the assistance of another person and which was associated with a blood glucose level <36 mg/dl and/or with recovery after oral carbohydrate, intravenous glucose, or glucagon administration.

FBG values and (for patients receiving 70/30) predinner blood glucose values, as well as hypoglycemic episodes, were recorded in a standardized diary. Hematologic, clinical chemistry, and HbA_{1c} values at baseline and 12 and 24 weeks were measured at a central laboratory (MDS, Hamburg, Germany); HbA_{1c} was measured by high-performance liquid chromatography (Bio-Rad Variant; Bio-Rad, Munich, Germany) traceable to the Diabetes Control and Complications Trial reference method, with a reference range of 4.8–6.7%. An eight-point glucose profile (before and 2 h after breakfast, lunch, and dinner; at bedtime; and at 3:00 A.M.) was obtained on 2 consecutive days before a visit at baseline and 2, 4, 8, 12, and 24 weeks. The baseline eight-point profile was performed while patients were receiving only glimepiride and metformin. Adverse events were noted by the investigator at every visit or telephone contact.

Efficacy and safety measures

The primary efficacy measure was the change in HbA_{1c} level from baseline to end point. Secondary efficacy measurements were HbA_{1c} level, mean FBG level, proportion of patients with FBG levels ≤100 mg/dl (≤5.6 mmol/l), proportion of patients with HbA_{1c} ≤7.0% and HbA_{1c} ≤7.0% with no nocturnal hypoglycemia, and mean blood glucose values from the eight-point profiles.

Safety measures were the proportion of patients with hypoglycemic events and the frequency of hypoglycemic events. Hypoglycemia was considered confirmed if documented by a blood glucose level <60 mg/dl (<3.3 mmol/l).

Statistical analyses

Statistical analyses were performed on the intent-to-treat population, defined as randomized patients who received at least one injection of insulin. Statistical testing was performed at a significance level of $\alpha = 0.05$. ANCOVAs were performed to compare changes in HbA_{1c} and secondary continuous variables between treatment groups. Adjusted means and corresponding two-sided 95% CIs were calculated. Categoric secondary variables were analyzed using Cochran-Mantel-Haenszel tests. Statistical analyses were performed using SAS software (version 8.2; SAS Institute, Cary, NC).

Sample size calculation

With a 1:1 randomization ratio and based on the assumption of a common SD of 1.3%, an absolute difference of 0.4% for HbA_{1c} reductions among treatment groups can be detected with an α error of 0.05 (two sided) and a β error of 0.2 with 167 patients per treatment group.

RESULTS — A total of 511 patients were screened: 371 patients were eligible for randomization, and 364 patients comprised the intent-to-treat population. There were 177 patients randomly assigned to glargine plus OAD and 187 to 70/30. Baseline demographic and clinical characteristics were similar between the treatment groups (Table 1). After randomization, 7 patients on glargine plus OAD (3 lost to follow-up and 4 other reasons) and 28 patients on 70/30 (12 unwilling to continue, 5 lack of efficacy, 2 lost to follow-up, and 9 other reasons) withdrew from the study.

Glycemic control

Over the 24-week treatment period, mean (±SD) HbA_{1c} levels decreased from 8.85 ± 0.98 to 7.15 ± 0.90% with glargine plus OAD and from 8.83 ± 0.87 to 7.49 ± 1.09% with 70/30 (Fig. 1*A*). Mean adjusted HbA_{1c} improvement was greater with glargine plus OAD (−1.64% [95% CI −1.51 to −1.78]) than with 70/30 (−1.31% [−1.17 to −1.44]). The adjusted mean between-treatment difference of −0.34% (−0.52 to −0.16%, P =

Table 1—*Baseline demographics and characteristics of the study population*

Characteristic	Insulin glargine plus OADs	Premixed insulin
n	177	187
Male/female (%)	61/39	57/43
Age (years)	60.9 ± 8.7	60.4 ± 9.1
Weight (kg)	85.1 ± 14.7	84.6 ± 14.2
BMI (kg/m^2)	29.5 ± 3.6	29.6 ± 3.6
Duration of diabetes (years)	9.9 ± 7.3	9.9 ± 6.4
Duration of OAD treatment (years)	7.0 ± 5.8	7.3 ± 5.5
C-peptide (ng/ml)	3.5 ± 2.1	3.5 ± 2.1
HbA_{1c} (%)	8.85 ± 0.98	8.83 ± 0.87
FBG (mg/dl)	171 ± 35	172 ± 38
FBG (mmol/l)	9.5 ± 1.9	9.6 ± 2.1

Data are means ± SD unless otherwise indicated. OAD refers to sulfonylurea plus metformin.

0.0003) significantly favored the glargine plus OAD group (Fig. 1*B*).

An HbA_{1c} level ≤7% was achieved by 49.4% of patients in the glargine plus OAD group compared with 39.0% in the 70/30 group ($P = 0.0596$ for the between-treatment difference). Significantly more patients on glargine plus OAD (45.5%) than on 70/30 (28.6%) reached an HbA_{1c} ≤7% without an episode of confirmed nocturnal hypoglycemia ($P = 0.0013$ for the between-treatment difference).

FBG levels decreased from 171 to 115 mg/dl (9.5 to 6.4 mmol/l) with glargine plus OAD and from 172 to 133 mg/dl (9.6 to 7.4 mmol/l) with 70/30. Improvement in FBG was significantly better with glargine plus OAD compared with 70/30 (adjusted mean between-treatment difference −17 mg/dl [−0.9 mmol/l]; 95% CI −24 to −10 mg/dl [–1.3 to −0.6 mmol/l], $P < 0.0001$). A greater proportion of patients reached an FBG level ≤100 mg/dl (≤5.6 mmol/l) with glargine plus OAD than with 70/30 (31.6 vs. 15.0%, $P = 0.0002$).

Diurnal (eight-point) glucose profiles were similar for both groups at baseline (before insulin initiation). Mean daily blood glucose level improved from 182 to 137 mg/dl (10.1 to 7.6 mmol/l) in the glargine plus OAD group compared with 184 to 151 mg/dl (10.2 to 8.4 mmol/l) in the 70/30 group ($P < 0.0001$ for between-treatment difference). At end point, the reduction from baseline was significantly greater with glargine plus OAD than with 70/30 for values obtained

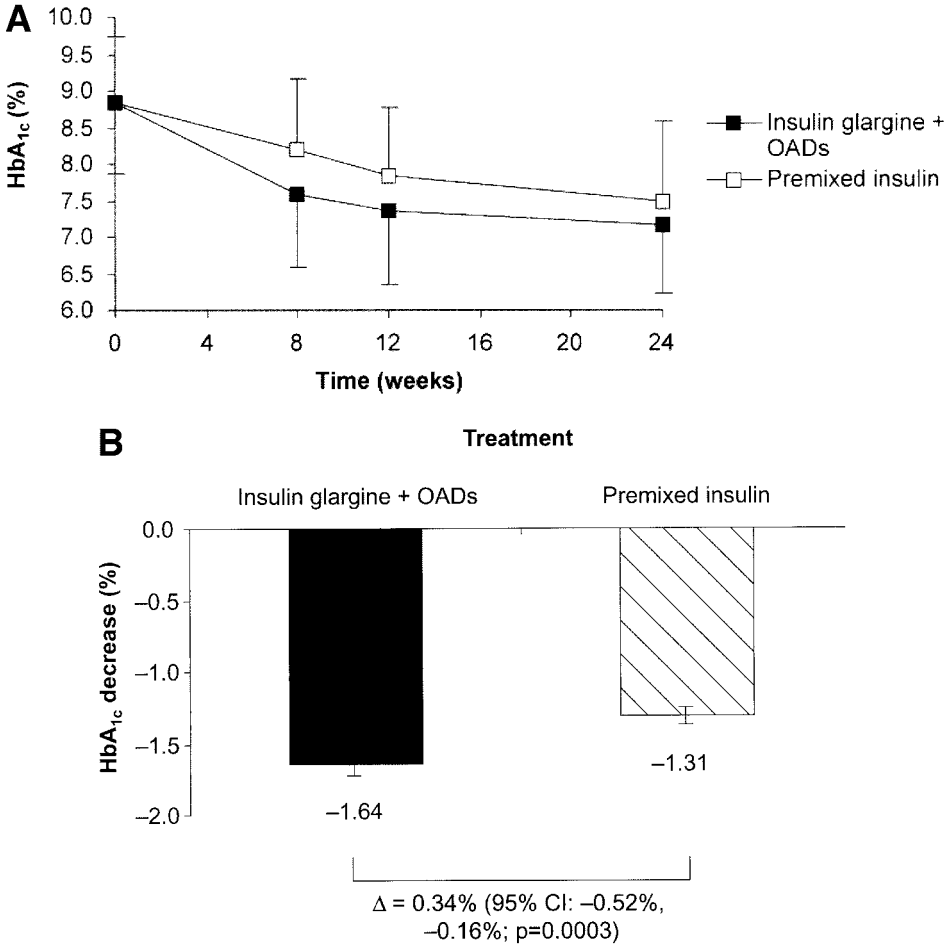

Figure 1—A: *Change in HbA_{1c} over 24 weeks (mean ± SD) in insulin glargine plus glimepiride and metformin (insulin glargine + OADs) and premixed insulin treatment groups.* B: *Improvement in HbA_{1c} (adjusted mean decrease from baseline [before insulin initiation] to end point ± SE).*

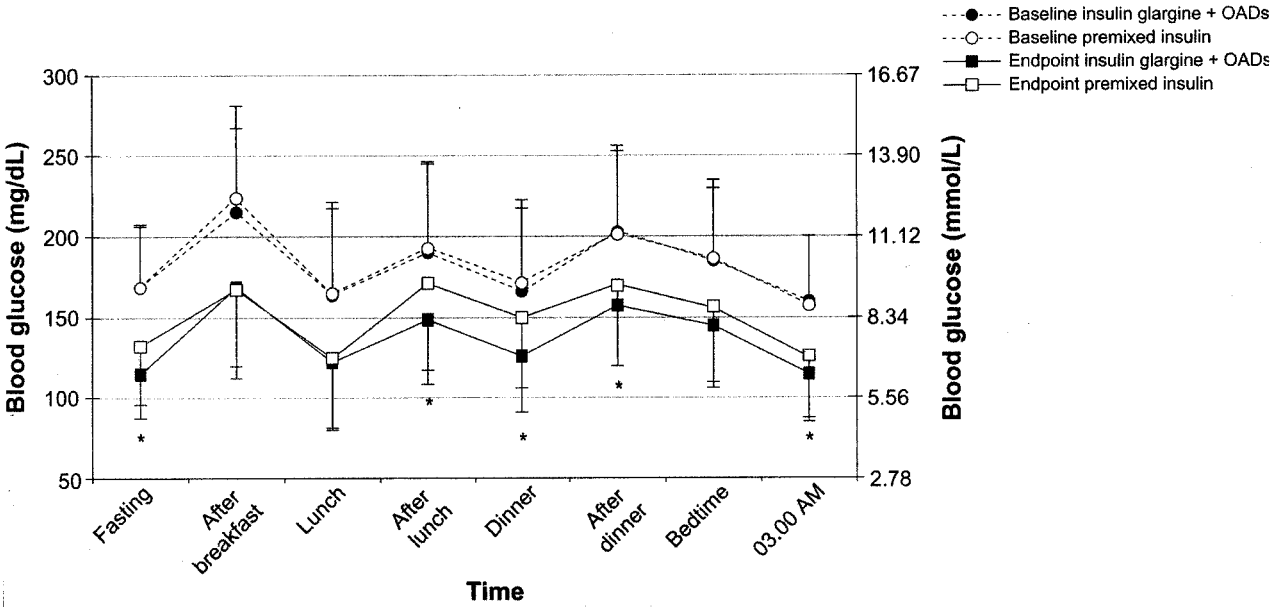

Figure 2—*Twenty-four–hour eight-point blood glucose profiles at baseline (before insulin initiation) and end point in insulin glargine plus glimepiride and metformin (insulin glargine + OADs) and premixed insulin treatment groups (*P < 0.05 for treatment comparison of changes from baseline to end point).*

at the fasting, postlunch, dinner, postdinner, and 3:00 A.M. time points (Fig. 2).

Insulin dose

Insulin dose increased over the study duration from a mean (±SD) daily starting dose of 9.9 ± 2.6 to 28.2 ± 15.2 IU at end point for insulin glargine. The prebreakfast dose of premixed insulin increased from the mean starting dose of 10.3 ± 2.5 to 33.5 ± 18.0 IU at end point, whereas the predinner dose increased from the mean starting dose of 10.3 ± 2.5 to 31.0 ± 16.1 IU at end point, resulting in more than twice as much daily insulin with 70/30 than with glargine plus OAD (64.5 vs. 28.2 IU). The mean daily dose was 3.4 ± 0.5 mg for glimepiride and 1,894.5 ± 475.1 mg for metformin.

Hypoglycemia

One hundred nine patients (61.6%) receiving glargine plus OAD and 127 patients (67.2%) receiving 70/30 experienced at least one hypoglycemic event ($P = 0.2838$). During treatment, the rate of confirmed hypoglycemic events, expressed as episodes per patient-years, was ~50% lower with glargine plus OAD than with 70/30 for the overall, symptomatic, and nocturnal categories (Table 2). Severe hypoglycemia was very uncommon in both treatment groups (Table 2).

Weight gain

Mean (±SD) weight gain in patients treated with glargine plus OAD and 70/30 was 1.4 ± 3.4 and 2.1 ± 4.2 kg, respectively ($P = 0.0805$ for between-group difference).

Adverse events

The incidence of adverse events was similar; 89 patients (50.3%) in the glargine plus OAD group and 92 patients (48.7%) in the 70/30 group experienced at least one adverse event. Most common were respiratory disorders (16%), nervous system disorders (10%), and gastrointestinal disorders (10%). A possible relationship to the study medication was reported for 10 adverse events in 8 glargine plus OAD patients and for 12 adverse events in 10 70/30 patients. Withdrawals due to adverse events occurred in one patient (0.6%) treated with glargine plus OAD and six patients (3.2%) treated with 70/30.

CONCLUSIONS— These results show that in patients with type 2 diabetes poorly controlled on oral therapy, adding a single injection of insulin glargine to glimepiride and metformin can provide more effective glycemic control than stopping OADs and starting twice-daily 70/30 insulin. The glargine plus OAD regimen enabled nearly 50% of patients to reach HbA_{1c} ≤7% without experiencing nocturnal hypoglycemia, whereas <30% of patients on 70/30 insulin achieved target HbA_{1c} ≤7% in the absence of nocturnal hypoglycemia.

The number of hypoglycemic events per patient-year and the number of events per patient were ~50% lower in the

Table 2—*Mean number of confirmed* hypoglycemic events per patient-years*

Type of hypoglycemia	Insulin glargine plus OADs	Premixed insulin	*P*
All	4.07	9.87	<0.0001
Symptomatic	2.62	5.73	0.0009
Nocturnal	0.51	1.04	0.0449
Severe†	0.00	0.05	0.0702

*Hypoglycemia was confirmed by blood glucose <60 mg/dl (3.3 mmol/l). †Severe hypoglycemia was defined as symptoms consistent with hypoglycemia that required the assistance of another person and were associated with either a blood glucose level <36 mg/dl (<2.0 mmol/l) or prompt recovery after oral carbohydrate or intravenous glucose or glucagon.

glargine plus OAD group than in the 70/30 group. The lower rate of hypoglycemia with the basal insulin regimen is of particular interest because fear of hypoglycemia remains one of the key obstacles to both initiating and optimizing insulin therapy (11–13). The difficulty of managing multiple injections and the associated requirement for multiple daily glucose measurements is another barrier to achieving recommended glycemic control targets (14). The glargine plus OAD regimen in this study required only a single daily injection and a single before-breakfast glucose test to guide therapy and, therefore, should be easy to use in clinical practice.

Since patients randomized to the 70/30 group did not receive glimepiride or metformin, this study compared two regimens for initiating insulin rather than two specific forms of insulin. However, previous studies using NPH insulin in combination with OADs did not show better glycemic control in terms of HbA_{1c} reduction in comparison to insulin monotherapy with premixed insulin (15–17). In the present study, insulin treatment initiated by adding insulin glargine to OADs resulted in a significantly greater improvement in glycemic control compared with 70/30 insulin alone. In clinical practice, OADs are often discontinued once a 70/30 insulin regimen is begun, but continuing metformin might be expected to improve the effectiveness of this regimen. Clearly, many questions remain regarding the initiation of insulin therapy in patients with type 2 diabetes. The current study provides efficacy and safety data pertaining to two commonly used insulin regimens. Further studies are required to provide physicians with additional guidance. These should include addressing the benefit of 70/30 insulin plus metformin combination to ascertain the level of influence of metformin on the results obtained in the insulin glargine–treated group. In addition, it would be of interest to compare the glargine plus OAD regimen with a rapid-acting analog plus NPH insulin as use of the latter insulin regimen becomes more widespread. The relative costs of treatment with all of these regimens, including the glucose testing required by each, should also be studied. Finally, despite the improvement in control achieved by adding insulin glargine to OADs, over one-half of patients in the glargine plus OAD group did not reach $HbA_{1c} \leq 7\%$. The relatively low total daily insulin dose in the glargine plus OAD group and the low rate of hypoglycemia with this regimen support the feasibility of continued titration to achieve target HbA_{1c} in more patients. Even so, some patients will require additional prandial injections of insulin to reach the $\leq 7\%$ HbA_{1c} target.

In conclusion, this study demonstrated that, for patients with type 2 diabetes who are inadequately controlled with metformin plus a sulfonylurea, adding a once-daily injection of insulin glargine is a simple method that is more effective in improving glycemic control than starting twice-daily injections of premixed insulin without oral agents.

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References

1. UK Prospective Diabetes Study (UKPDS) Group: Intensive blood-glucose control with sulfonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). *Lancet* 352:837–853, 1998
2. Ohkubo Y, Kishikawa H, Araki E, Miyata T, Isami S, Motoyoshi S, Kojima Y, Furuyoshi N, Shichiri M: Intensive insulin therapy prevents the progression of diabetic microvascular complications in Japanese patients with non-insulin-dependent diabetes mellitus: a randomized prospective 6-year study. *Diabetes Res Clin Pract* 28:103–117, 1995
3. The Diabetes Control and Complications Trial Research Group: The absence of a glycemic threshold for the development of long-term complications: the perspective of the Diabetes Control and Complications Trial. *Diabetes* 45:1289–1298, 1996
4. Stratton IM, Adler AI, Neil HA, Matthews DR, Manley SE, Cull CA, Hadden D, Turner RC, Holman RR: Association of glycemia with macrovascular and microvascular complications of type 2 diabetes (UKPDS 35): prospective observational study. *BMJ* 321:405–411, 2000
5. European Diabetes Policy Group 1999: A desktop guide to type 2 diabetes mellitus. *Diabet Med* 16:716–730, 1999
6. American Diabetes Association: Standards of medical care for patients with diabetes mellitus (Position Statement). *Diabetes Care* 25:S33–S49, 2002
7. Koivisto V, Tuominen J, Ebeling P: Lispro Mix25 insulin as premeal therapy in type 2 diabetic patients. *Diabetes Care* 22:459–462, 1999
8. Hauner H, Koster L, von Ferber L: Prevalence of diabetes mellitus in Germany 1998–2001. *Dtsch Med Wochenschr* 128: 2632–2637, 2003
9. Lepore M, Pampanelli S, Fanelli C, Porcellati F, Bartocci L, Di Vincenzo A, Cordoni C, Costa E, Brunetti P, Bolli GB: Pharmacokinetics and pharmacodynamics of subcutaneous injection of long-acting human insulin analog glargine, NPH insulin, and ultralente human insulin and continuous subcutaneous infusion of insulin lispro. *Diabetes* 49:2142–2148, 2000
10. Heinemann L, Linkeschova R, Rave K, Hompesch B, Sedlak M, Heise T: Time-action profile of the long-acting insulin analog glargine (HOE901) in comparison with those of NPH insulin and placebo. *Diabetes Care* 23:644–649, 2000
11. Korythowski M: When oral agents fail: practical barriers to starting insulin. *Int J Obes Relat Metab Disord* 26:S18–S24, 2002
12. Johnson R, Hauber B, Bolinder B: Trade-offs between glucose control and hypoglycemia in different patient types: results of a 5-country physician survey (Abstract). *Diabetes* 52 (Suppl. 1):A264, 2003
13. Fritsche A, Häring H-U, Tögl E, Schweitzer M-A, the HOE901/4001

Study Group: Treat-to-target with add-on basal insulin: can glargine reduce barrier to target attainment? (Abstract). *Diabetes* 52 (Suppl. 1):A119, 2003
14. Cefalu WT: Evaluation of alternative strategies for optimizing glycemia: progress to date. *Am J Med* 113 (Suppl. 6A):23S–35S, 2002
15. Yki-Järvinen H, Kauppila M, Kujansuu E, Lahti J, Marjanen T, Niskanen L, Rajala S, Ryysy L, Salo S, Seppälä P, Tulokas T, Viikari J, Karjalainen J, Taskinen M-R: Comparison of insulin regimens in patients with non-insulin-dependent diabetes mellitus. *N Engl J Med* 327:1426–1433, 1992
16. Wolffenbuttel BH, Sels JP, Rondas-Colbers GJ, Menheere PP, Nieuwenhuijzen Kruseman AC: Comparison of different insulin regimens in elderly patients with NIDDM. *Diabetes Care* 19:1326–1332, 1996
17. Olsson PO, Lindstrom T: Combination-therapy with bedtime NPH insulin and sulphonylureas gives similar glycemic control but lower weight gain than insulin twice daily in patients with type 2 diabetes. *Diabetes Metab* 28:272–277, 2002