

# Long-term Glycemic Control After 6 Months of Basal Insulin Therapy

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**T**ype 2 diabetes mellitus (T2DM) is characterized by declining  $\beta$ -cell function in the presence of increasing hyperglycemia and relatively constant insulin resistance.<sup>1</sup> This process begins early in the natural course of the disease, accelerates markedly after reaching a compensatory threshold, and drives disease progression.<sup>1</sup> Accumulating evidence suggests that this decline can be slowed or even reversed, potentially at an early stage of disease.<sup>2</sup> Studies have shown that short-term intensive insulin therapy at the time of diagnosis can lead to rapid improvement in  $\beta$ -cell function and maintenance of glycemic control for months after therapy is stopped.<sup>3-6</sup>

Recently, investigators in China and Taiwan reported the results from 2 independent randomized controlled trials in patients with newly diagnosed T2DM. Both trials compared the effects of short-term intensive insulin therapy with those of oral antidiabetic agents (OADs) on glycemic control and  $\beta$ -cell function: insulin therapy led to more effective glycemic control and significantly greater improvement in  $\beta$ -cell function than did oral antidiabetic agents.<sup>7,8</sup> However, data on the effects of short-term insulin on maintaining long-term glycemic control are scarce, especially in patients with severe hyperglycemia.

When a patient presents with new-onset T2DM with severe hyperglycemia, the optimal treatment is aggressive insulin therapy.<sup>9,10</sup> Once symptomatic relief has been achieved, it may be possible to withdraw insulin and shift to oral agents. We hypothesized that continuous insulin therapy in patients with new-onset T2DM with severe hyperglycemia may achieve prolonged glycemic control. We designed a 6-month interventional trial to compare the benefits of basal insulin therapy with those of OADs; patients would pursue one course or the other after correction of the glucose toxicity with a short period of intensive insulin therapy. The current study is the continuation of our previous published trial<sup>8</sup> to evaluate the long-term maintenance (5 years) of glycemic control in newly diagnosed individuals with T2DM with severe hyperglycemia. We also investigated the possible mechanisms responsible for the development of long-term glycemic remission.

## ABSTRACT

### Objectives

To compare the effects of a 6-month course of insulin therapy versus oral antidiabetic drugs (OADs) on long-term (5-year) glycemic control in patients newly diagnosed with type 2 diabetes mellitus (T2DM) with severe hyperglycemia.

### Study Design

5 years' follow-up of a randomized controlled trial.

### Methods

Newly diagnosed patients with T2DM and severe hyperglycemia were hospitalized and treated with intensive insulin injections for 10 to 14 days. Fifty patients were randomized to receive either insulin injections or OADs for an additional 6 months. Subjects were followed for 5 years to evaluate long-term glycemic control. We compared the glycated hemoglobin (A1C) levels of the treatment groups and the proportion of patients in each group who reached the treatment targets. We also examined the remission rate (A1C  $\leq$ 6.5% without antidiabetic medication) at the end of the 5 years. The mechanisms of improved glycemic control and possible mechanism of remission were also investigated.

### Results

At 5 years, A1C levels remained lower in the insulin group than in the OAD group ( $6.49 \pm 0.72\%$  vs  $7.72 \pm 1.06\%$ ;  $P = .012$ ). The proportion of subjects with A1C levels  $\leq$ 6.5% was significantly higher in the insulin group than in the OAD group (63.6% vs 23.5%;  $P = .013$ ). The remission rate was 27.3% in the insulin group and 5.9% in the OAD group ( $P = .048$ ).

### Conclusions

This randomized trial demonstrated that a 6-month course of insulin therapy led to better 5-year glycemic control, reflected by lower A1C levels, than did oral antidiabetic agent therapy. Moreover, the insulin-treated group had a significantly higher rate of remission from diabetes.

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### Take-Away Points

When a patient presents with new-onset type 2 diabetes mellitus (T2DM) with severe hyperglycemia, the optimal treatment is aggressive insulin therapy. Some patients may be withdrawn from insulin and shifted to oral antidiabetic agents after the symptoms decline in 10 to 14 days. We designed an interventional trial to compare the effects of 6 further months of insulin therapy versus oral antidiabetic drugs (OADs) on long-term (5-year) glycemic control in these patients. We found that a 6-month course of insulin therapy led to better 5-year glycemic control than did OAD therapy in newly diagnosed T2DM patients with severe hyperglycemia.

### Outpatient Clinic Follow-up

All subjects were discharged after 10 to 14 days of intensive insulin therapy, and were subsequently randomized to either continue with insulin treatment or shift to OADs. Subjects were then followed as outpatients; they visited our clinic every 2 weeks for the first 2 months,

then every 4 weeks for another 4 months.

Subjects in the insulin group were instructed in the technique of glucose monitoring. Two-thirds of the daily dose was administered before breakfast and the remaining third was administered at bedtime. Both morning and bedtime insulin doses were titrated every 3 days to achieve target FPG values between 90 and 130 mg/dL.

The titration method of OADs in our protocol was modified from that of the Steno-2 Study published in 2003.<sup>10</sup> As the initial step, overweight or obese patients (defined as having a body mass index [BMI] >25) received metformin (daily doses ranged from 500 mg once a day to 500 mg 3 times a day), and lean patients received a drug in the sulfonylurea class, gliclazide-MR (with doses ranging from 30 mg to 90 mg per day). The dosage was titrated based on FPG results on the visiting day to achieve target values between 90 and 130 mg/dL. As the second step, metformin was added to the regimen of the lean patients, and gliclazide-MR to the regimens of overweight and obese patients. As a possible third step, gliclazide-MR could be up-titrated to a maximum dose of 120 mg per day and metformin to 2550 mg per day (with split dosing).

## METHODS

### Study Design and Subjects

This study was a randomized, open-label, controlled trial and was designed a priori in 2 parts. The first part was a 6-month interventional study to test the effects of insulin on insulin resistance and  $\beta$ -cell function in patients with newly diagnosed T2DM with severe hyperglycemia.<sup>8</sup> The second part was a 5-year follow-up study to test the effects of insulin on the durability of long-term glycemic control, which was conducted in response to an inquiry from our Institutional Review Board. The mechanisms of improved glycemic control and possible mechanism of remission were also investigated.

We recruited consecutive newly diagnosed T2DM patients with severe hyperglycemia (fasting plasma glucose >300 mg/dL or random plasma glucose >400 mg/dL) who had been admitted to Taipei Veterans General Hospital. Randomization was performed after 10 to 14 days of intensive insulin therapy by using an insulin-treatment to OAD-treatment ratio of 3:2. Therefore, 30 patients were randomly assigned to the insulin group and 20 to the OAD group. Forty-two patients completed the 6-month intervention, and 5-year follow-up data were available for 39 patients (Figure 1). The study was approved by the Institutional Review Board of Taipei Veterans General Hospital, and written informed consent was obtained from all participants.

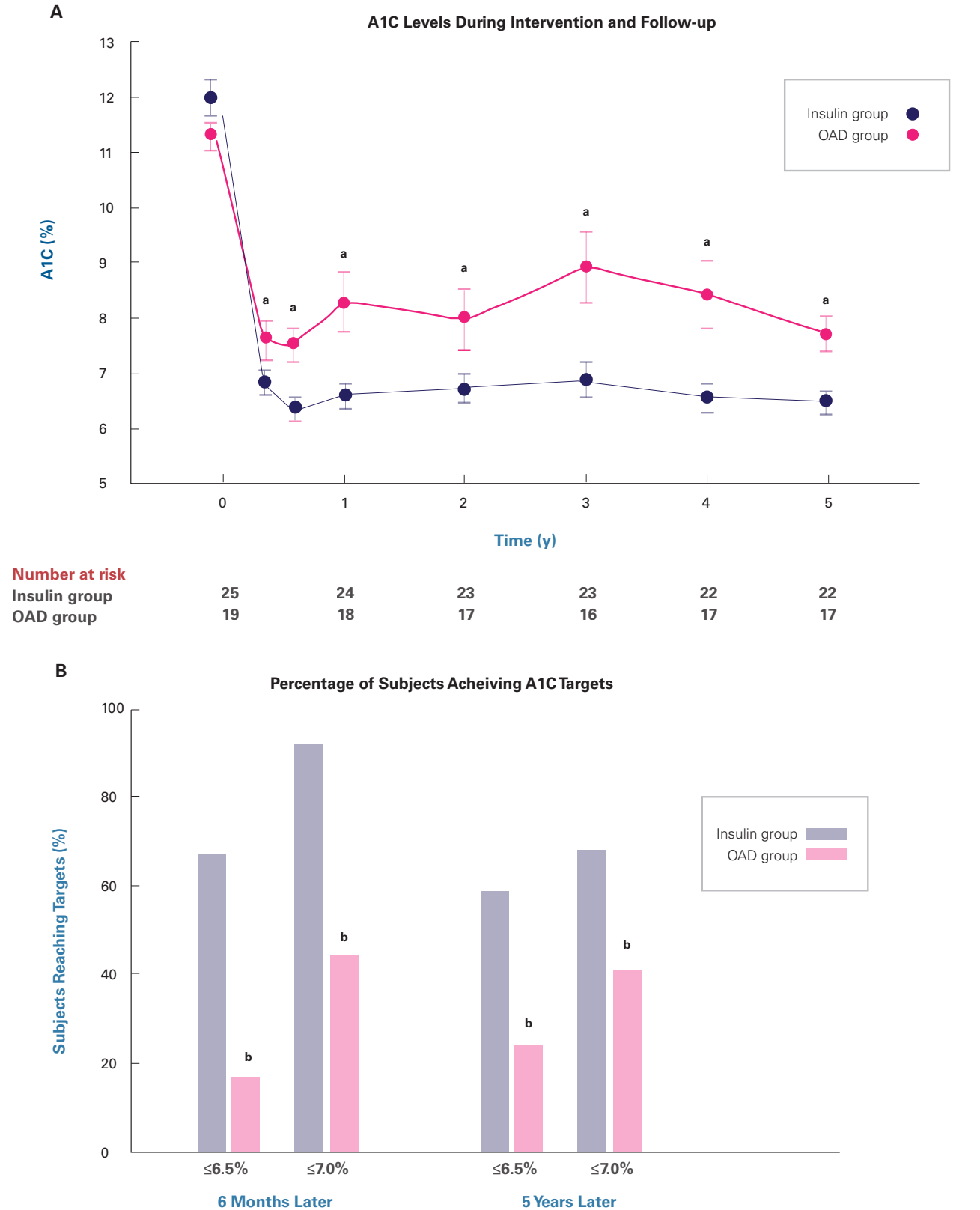
### Hospitalization Procedures

Bedtime neutral protamine Hagedorn (NPH) insulin (Insulatard, Novo Nordisk, Denmark) and regular insulin taken before meals (Actrapid, Novo Nordisk, Denmark) were used for intensive insulin therapy. The target glucose levels were fasting blood glucose (FBG) 90 to 130 mg/dL and bedtime blood glucose 100 to 160 mg/dL.<sup>9</sup> All subjects received a 75g oral glucose tolerance test (OGTT) when their fasting blood glucose levels were between 100 and 140 mg/dL. Blood samples were collected for glucose and insulin analysis at 30, 60, 90, and 120 minutes, and for C-peptide analysis at 120 minutes.

### Clinical Examination

Glycated hemoglobin (A1C) measurements were performed at 3 and 6 months, and the OGTT was repeated 6 months after randomization. We stopped pharmacologic treatment approximately 12 hours (metformin) and 24 hours (gliclazide-MR and insulin) before performing the OGTT. Areas under the glucose and insulin curves during the OGTT were calculated by the trapezoid rule. Early-phase insulin secretion (insulinogenic index) was calculated as the ratio between the incremental plasma insulin and glucose concentrations during the first 30 minutes of the OGTT. Total insulin secretion was calculated as the ratio between the incremental areas under the insulin and glucose curves during the OGTT. The Matsuda index was calculated for insulin resistance as previously reported.<sup>11</sup> Homeostasis model assessment was used to estimate insulin resistance (HOMA-IR) and  $\beta$ -cell function (HOMA-B).<sup>12</sup>

**Figure 1.** Glycemic Control in the Insulin and Oral Antidiabetic Agents Groups



(A) The glycated hemoglobin (A1C) changes (mean ± SE) in both groups during the study period and follow-up period. (B) The proportion of patients with A1C level ≤6.5% or 7.0% at 6 months and 5 years.

### Follow-up Examination

After 6 months of randomization, patients in the insulin group stopped insulin and started OADs for further management. The dose titration procedure was the same as that used during the intervention period in the OAD group. After 12 months, all patients were treated in our clinics according to national guidelines. The dosage was titrated based on the A1C value to achieve a target value  $-6.5\%$ . A third medication was considered when the A1C value was greater than  $7.5\%$ . Our protocol also recommended decreasing the dose of medication when the A1C value was less than  $6.0\%$  and the FPG level was less than  $100\text{ mg/dL}$ . All subjects were continually followed in our clinics for 5 years to evaluate long-term glycemic control.

### Outcomes

The overall goal of this follow-up study was to investigate long-term glycemic control. The primary end points were the A1C levels and the proportion of patients who reached the treatment targets (A1C  $-6.5\%$  or  $-7.0\%$  at 5 years) between the treatment groups. The secondary end points were the remission rate (A1C  $-6.5\%$  without anti-diabetic medication) at the end of the 5 years of follow-up, and severe hypoglycemia, defined as a recorded blood glucose value less than  $40\text{ mg/dL}$ . We also examined the possible mechanism for remission from the biochemical measurements over the course of interventions.

### Statistical Analyses

This is a 5-year follow-up study from a randomized controlled trial. We analyzed the outcomes of the intent-to-treat population defined as all randomized patients who had received the second OGTT at the end of intervention. Statistical analyses were performed using SPSS for Windows version 18.0 (SPSS, Inc, Chicago, IL). Normally distributed and continuous variables are presented as mean  $\pm$  SD, and non-normally distributed variables are expressed as median (interquartile range). The paired Student's *t* test was used to analyze differences from baseline to end point, and the independent Student's *t* test was used to compare differences between the treatment arms. Changes from baseline in A1C, insulin dose, OAD dose, body weight, and hypoglycemic events were analyzed using 1-way analysis of variance (ANOVA). A Mann-Whitney U test was used to analyze the non-normally distributed variables, and  $\chi^2$  tests were used to analyze the differences in remission rates between the 2 intervention groups. A1C levels were measured every 3 to 4 months, and the median value was determined for each year. All doses of sulfonylureas were calculated as

equivalent gliclazide dose at the last visit. The average doses of insulin and OADs were calculated as total dose divided by patient number in each group. A *P* value of less than .05 was considered statistically significant.

## RESULTS

### Demographic, Clinical, and Biochemical Characteristics

Demographic, clinical, and biochemical characteristics of the patients at baseline, at the end of intervention (6 months), and at the end of follow-up (5 years) are shown in **Table 1**. The baseline data presented in Table 1, except for the fasting plasma glucose (FPG) levels, were obtained after 10 to 14 days of intensive insulin therapy. The mean age was  $57.5 \pm 16.3$  years; mean body weight was  $72.4 \pm 17.3$  kg; mean BMI was  $26.5 \pm 5.3\text{ kg/m}^2$ ; mean peak plasma glucose was  $531 \pm 156\text{ mg/dL}$ ; mean FPG was  $333 \pm 88\text{ mg/dL}$ ; and mean A1C was  $11.77 \pm 2.08\%$ .

### Glycemic Control

Glycemic control, including A1C values and FPG levels, was similar at baseline in the 2 groups. At the end of the 6-month intervention, the mean FPG was  $122.6 \pm 29.5\text{ mg/dL}$  in the insulin group and  $130.2 \pm 19.9\text{ mg/dL}$  in the OAD group, a difference that was not statistically significant ( $P = .333$ ). However, at the end of 5 years, the FPG was significantly lower in the insulin group than the OAD group ( $120.3 \pm 22.0$  vs  $145.0 \pm 33.6\text{ mg/dL}$ ;  $P = .019$ ).

Figure 1A shows the A1C changes in both groups during the study period and follow-up visits. After 6 months of intervention, the A1C level was significantly lower in the insulin group than in the OAD group ( $6.33 \pm 0.70\%$  vs  $7.50 \pm 1.50\%$ ;  $P < .001$ ), and the differences were maintained through to the end of 5 years of follow-up ( $6.49 \pm 0.72\%$  vs  $7.72 \pm 1.06\%$ ;  $P = .001$ ).

Figure 1B shows the proportion of subjects in each group with an A1C level  $-6.5\%$  or  $-7.0\%$  at 6 months and 5 years. The proportion with an A1C level  $-6.5\%$  was significantly higher in the insulin group than in the OAD group at 6 months ( $66.7\%$  vs  $16.7\%$ ;  $P = .001$ ) and at 5 years ( $63.6\%$  vs  $23.5\%$ ;  $P = .013$ ). The proportion with an A1C level  $-7.0\%$  was significantly higher in the insulin group than in the OAD group at 6 months ( $91.6\%$  vs  $44.4\%$ ,  $P = .008$ ), but non-significantly higher at 5 years ( $68.2\%$  vs  $41.2\%$ ;  $P = .092$ ).

### Antidiabetic Medication

**Table 2** shows the details of medications given during

**■ Table 1.** Demographic, Clinical, and Biochemical Characteristics at Baseline, End of Intervention, and 5 Years After Randomization

	Baseline		End of intervention		5 Years After Randomization	
	Insulin Group	OAD Group	Insulin Group	OAD Group	Insulin Group	OAD Group
Number	25	19	24	18	22	17
Age (years)	57.2 ± 8.3	58.8 ± 12.5	57.9 ± 8.5	59.6 ± 12.6	62.2 ± 15.2	63.6 ± 20.1
Sex (male:female)	19:6	13:6	19:5	13:5	17:5	13:4
Body weight (kg)	71.4 ± 10.6	71.7 ± 21.3	73.1 ± 11.6	73.4 ± 16.9	69.6 ± 11.4	72.5 ± 18.8
BMI (kg/m <sup>2</sup> )	26.1 ± 4.7	27.0 ± 6.1	26.7 ± 3.6	27.4 ± 4.6	25.2 ± 3.3	27.2 ± 4.9
Fasting plasma glucose (mg/dL)	345.0 ± 82.2	329.2 ± 24.0	122.6 ± 29.5 <sup>a</sup>	130.2 ± 19.9 <sup>a</sup>	120.3 ± 22.0 <sup>a,b</sup>	145.0 ± 33.6 <sup>a,b</sup>
A1C (%)	11.89 ± 1.91	11.33 ± 1.57	6.33 ± 0.70 <sup>a,b</sup>	7.50 ± 1.50 <sup>a,c</sup>	6.49 ± 0.72 <sup>a,b</sup>	7.72 ± 1.06 <sup>a,b</sup>
Systolic BP (mm Hg)	125.4 ± 13.4	130.7 ± 12.9	129.2 ± 12.4	130.0 ± 15.7	130.6 ± 12.6	137.4 ± 14.8
Diastolic BP (mm Hg)	74.2 ± 10.6	78.5 ± 8.1	76.1 ± 10.0	79.7 ± 11.3	74.8 ± 10.4	81.5 ± 10.7
Total cholesterol (mg/dL)	193.1 ± 54.8	184.7 ± 39.5	175.4 ± 44.1	183.6 ± 40.0	172.4 ± 26.6	178.3 ± 34.0
HDL cholesterol (mg/dL)	45.9 ± 15.1	45.7 ± 12.7	48.5 ± 11.4	47.6 ± 14.9	43.9 ± 8.8	45.3 ± 11.7
Triglyceride (mg/dL)	136 (97-197)	131 (85-192)	112 (82-151)	149 (82-237)	125 (70-171)	98 (58-171)
Serum creatinine (mg/dl)	0.98 ± 0.34	0.92 ± 0.37	0.97 ± 0.27	0.99 ± 0.31	0.99 ± 0.27	0.98 ± 0.21
Urine albumin-to-creatinine ratio (mg/g)	12.0 (5.2-40.4)	18.7 (10.6-49.6)	11.9 (7.0-31.4)	20.6 (9.5-42.6)	6.3 (4.0-27.8) <sup>c</sup>	35.4 (14.4-175.9) <sup>b</sup>

A1C indicates glycated hemoglobin; BMI, body mass index; BP, blood pressure; FPG, fasting plasma glucose; HDL, high-density lipoprotein; OAD, oral anti-diabetic drug.

Triglyceride and Urine albumin-to-creatinine ratio were presented as median with interquartile range.

<sup>a</sup>*P* <.05 compared with baseline; <sup>b</sup>*P* <.05 between groups.

the intervention and follow-up periods. During the study period, the insulin dose was decreased from a mean of 26.4 ± 10.5 IU/day to 16.8 ± 11.0 IU/day. The OAD dosage was increased gradually and titrated to a mean of 54.5 ± 22.5 mg/day of gliclazide-MR and 884 ± 416 mg/day of metformin at the end of the intervention. Five years after randomization, the dosage of gliclazide-MR (9.5 ± 22.5 vs 43.9 ± 46.8 mg/day; *P* = .009) and metformin (289 ± 535 vs 1004 ± 942 mg/day; *P* = .010) was significantly lower in the insulin group, but the insulin dose (13.4 ± 20.6 vs 11.6 ± 23.0 IU/day; *P* = .818) was not significantly different between the 2 groups.

**Remission Status**

At the end of 5 years, the remission rate was 27.3% (6 of 22) in the insulin group and 5.9% (1 of 17) in the OAD group (*P* = .048). **Table 3** shows the changes in biochemical measurements over the course of the intervention period, for those who did and did not achieve remission in both the insulin and OAD groups. The plasma glucose and insulin excursions during each OGTT in these 3 groups are illustrated in **Figure 2**. At 6 months, compared with non-remission patients in the OAD group, nearly all parameters of glycemic control and β-cell function were more favorable in the insulin-treated patients with remission. When the clinical characteristics of patients with and without remission in the insulin group were compared,

patients with glycemic remission had higher insulinogenic index scores after 10 to 14 days of intensive insulin therapy than those without glycemic remission. They also had lower FPG levels, A1C values, and HOMA-IR values, and higher insulin sensitivity (Matsuda index), after the 6-month intervention.

**Other Clinical Data During Follow-up**

No severe hypoglycemic events were recorded in either group during the follow-up period, nor were any significant changes or differences between the groups in body weight observed during that time. After 5 years, urine albumin-to-creatinine ratio was significantly lower in the insulin group (Table 1). The other clinical features were similar in the 2 treatment groups at baseline, at the end of the intervention, and after 5 years of follow-up.

**DISCUSSION**

The study showed that the desired glycemic control was successfully achieved by intensive insulin therapy for 10 to 14 days in cases of newly diagnosed T2DM with severe hyperglycemia. Compared with 6 months of OAD therapy, a 6-month course of further insulin therapy was more effective in achieving near-normal A1C levels and maintaining glycemic control for up to 5 years of follow-

**Table 2.** Medication Details During Intervention and Follow-Up Periods in Both Groups

	End of Intervention Period		5 Years After Randomization	
	Insulin Group	OAD Group	Insulin Group	OAD Group
<b>N</b>	24	18	22	17
<b>Medication</b>				
Final gliclazide dose (mg/day)	0	54.5 ± 22.5 <sup>a</sup>	9.5 ± 22.5	43.9 ± 46.8 <sup>a</sup>
Final metformin dose (mg/day)	0	884 ± 416 <sup>a</sup>	289 ± 535	1004 ± 535 <sup>a</sup>
Other OADs (%)	0	0	2 (9.1%)	5 (31.3%)
Insulin dose (units/day)	16.8 ± 11.0	0.9 (1 patient)	13.4 ± 20.6	11.6 ± 23.0
Insulin only (N, %)	20 (83.3%)	0	4 (18.2%)	1 (6.3%)
OADs only (N, %)	0	17 (94.4%)	7 (31.8%)	9 (56.3%)
Insulin + OADs (N, %)	0	1 (5.6)	5 (22.7%)	6 (37.5%)
Remission rate (N, %)	4 (16.7%)	0	6 (27.3%)	1 (6.3%) <sup>a</sup>

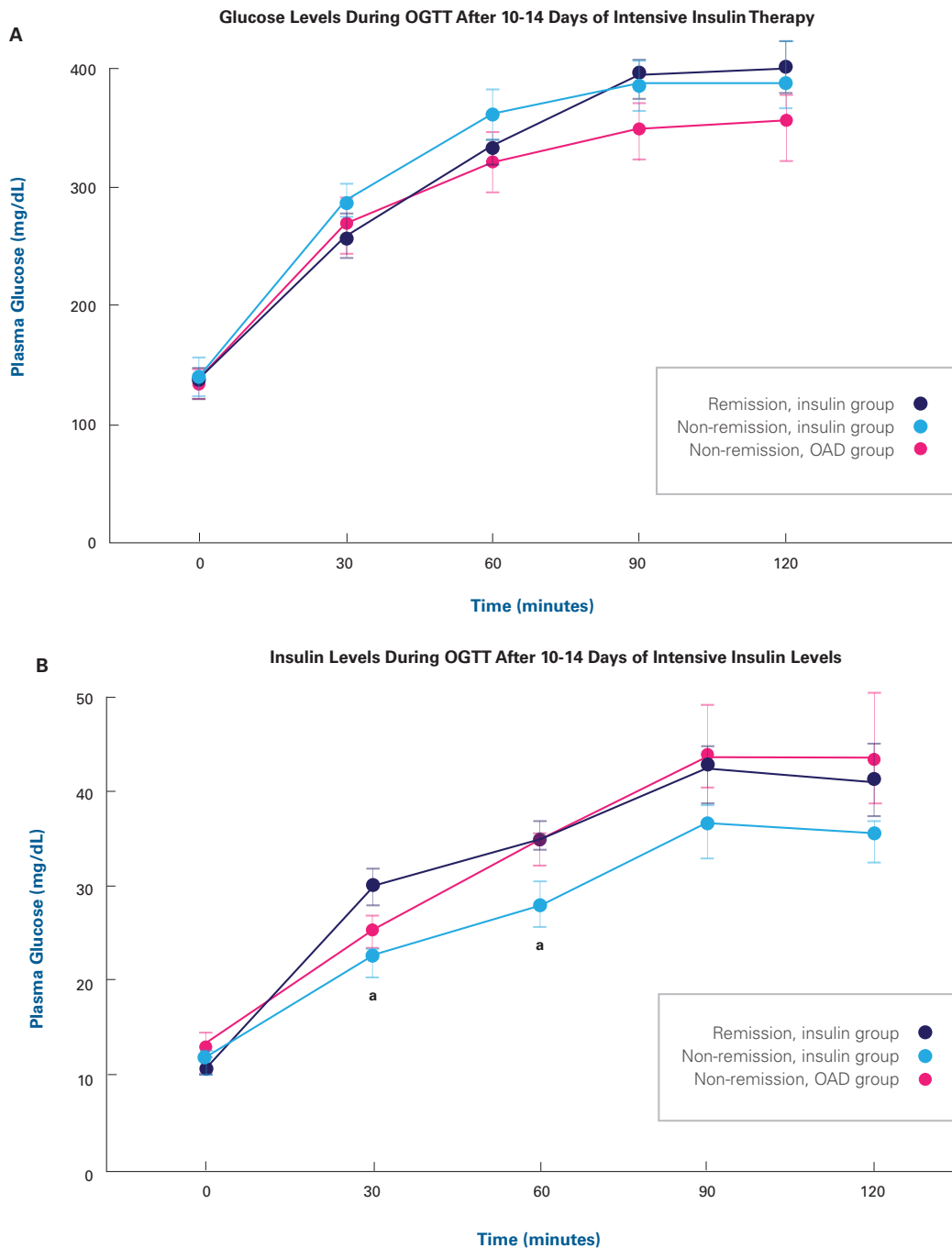
OAD indicates oral anti-diabetic drug.  
 Remission rate was defined as A1C ≤6.5% without anti-diabetic medication.  
<sup>a</sup>P <.05 compared between groups.

**Table 3.** Clinical Characteristics, Measures of Glycemia and Insulin Secretion During OGTT Among Our Study Patients

	Remission Insulin Group	Non-remission Insulin Group	Non-remission OAD Group
<b>N</b>	6	16	16
<b>Sex (male:female)</b>	4:1	12:4	12:4
<b>Age (years)</b>	62.0 ± 17.2	56.5 ± 15.8	57.7 ± 19.1
<b>Peak plasma glucose (mg/dL)</b>	622.0 ± 243.5	559.2 ± 105.6	487.7 ± 151.4
<b>Fasting plasma glucose (mg/dL)</b>	398.5 ± 62.3	335.3 ± 85.3	319.3 ± 107.1
<b>A1C (%)</b>	11.08 ± 1.55	12.11 ± 2.51	11.30 ± 1.43
<b>After 10-14 days of intensive insulin therapy</b>			
Body weight (kg)	73.7 ± 8.7	70.5 ± 9.7	72.7 ± 24.4
BMI (kg/m <sup>2</sup> )	26.1 ± 3.6	24.6 ± 2.7	27.0 ± 7.0
HOMA-IR	3.64 ± 0.56	4.03 ± 1.55	4.37 ± 2.72
HOMA-Beta (%)	47.8 ± 5.45	53.2 ± 20.6	63.8 ± 29.1
Glucose AUC (mg-hr-dL <sup>-1</sup> )	633.2 ± 60.7	651.1 ± 126.9	607.3 ± 122.0
Insulin AUC (μU-hr-mL <sup>-1</sup> )	66.4 ± 7.2	55.3 ± 18.5	66.8 ± 38.6
Insulin <sub>0-30</sub> /Glucose <sub>0-30</sub> (μU-mg <sup>-1</sup> )	1.78 ± 0.62	1.04 ± 0.84 <sup>a</sup>	1.51 ± 1.45
ΔInsulin <sub>AUC</sub> /ΔGlucose <sub>AUC</sub> (μU-mg <sup>-1</sup> )	1.35 ± 0.35	1.08 ± 0.80	1.29 ± 1.21
Matsuda index	101.7 ± 3.4	114.3 ± 15.9	115.2 ± 30.2
<b>After 6 months of further insulin therapy</b>			
Body weight (kg)	69.2 ± 8.4	70.3 ± 12.5	72.3 ± 16.5
BMI (kg/m <sup>2</sup> )	24.9 ± 3.2	25.7 ± 3.5	26.8 ± 4.5
Fasting plasma glucose (mg/dL)	100.3 ± 18.7	127.9 ± 21.8 <sup>a</sup>	131.3 ± 21.6 <sup>a</sup>
A1C (%)	5.68 ± 0.31	6.46 ± 0.72 <sup>a</sup>	7.81 ± 2.29 <sup>a</sup>
HOMA-IR	2.82 ± 1.62	5.37 ± 3.14 <sup>a</sup>	4.95 ± 3.93
HOMA-Beta (%)	114.3 ± 59.1	86.4 ± 34.5	86.9 ± 61.1
Glucose AUC (mg-hr-dL <sup>-1</sup> )	365.5 ± 44.1	513.4 ± 69.3 <sup>a</sup>	520.6 ± 89.3 <sup>a</sup>
Insulin AUC (μU-hr-mL <sup>-1</sup> )	149.0 ± 71.7	142.4 ± 52.1	113.5 ± 67.3 <sup>a</sup>
Insulin <sub>0-30</sub> /Glucose <sub>0-30</sub> (μU-mg <sup>-1</sup> )	6.00 ± 4.05	5.30 ± 4.22	2.83 ± 1.72 <sup>a</sup>
ΔInsulin <sub>AUC</sub> /ΔGlucose <sub>AUC</sub> (μU-mg <sup>-1</sup> )	7.73 ± 4.28	5.08 ± 3.59	3.44 ± 1.92 <sup>a</sup>
<b>Matsuda index</b>	104.4 ± 27.5	82.6 ± 15.8 <sup>a</sup>	93.5 ± 22.8

A1C indicates glycated hemoglobin; AUC, area under the curve; BMI, body mass index; HOMA-IR, homeostasis model assessment for insulin resistance; and HOMA-Beta, β-cell function.  
<sup>a</sup>P <.05 compared with remission insulin-group.

**Figure 2.** Mean  $\pm$  SE for Plasma Glucose and Insulin Concentrations During the Oral Glucose Tolerance Test



Mean  $\pm$  SE for plasma glucose (A) and insulin (B) concentrations during the oral glucose tolerance test (OGTT) after 10 to 14 days of intensive insulin therapy in each group.

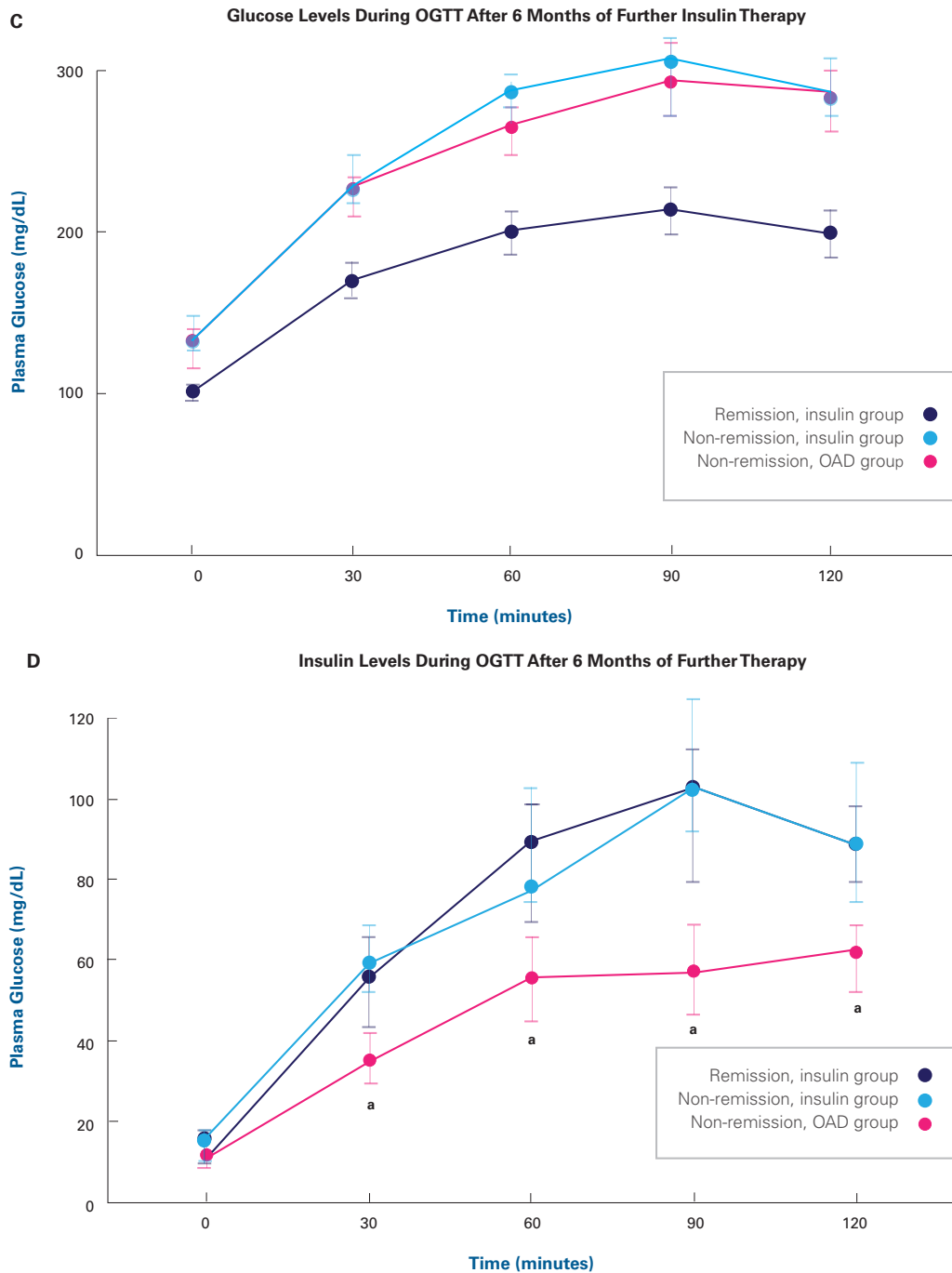
\* $P < .05$  compared with the patients with remission in the insulin group.

up. The restoration of early-phase insulin secretion after 10 to 14 days of intensive insulin therapy and sustained glycemic control for 6 months could be the mechanism responsible for long-term glycemic remission.

The underlying defects in patients with T2DM are insulin resistance and impaired insulin secretion. Insulin re-

sistance may develop decades before the onset of diabetes, reach a plateau at diabetes diagnosis, and then remain stable in the long term.<sup>13,14</sup> When T2DM is diagnosed along with severe hyperglycemia, if the hyperglycemia has existed for an extended duration, the patient may have undergone  $\beta$ -cell decompensation due to exposure of  $\beta$ -cells to

**Figure 2.** Glycemic Control in the Insulin and Oral Antidiabetic Agents Groups



Mean±SE for plasma glucose (C) and insulin (D) concentrations during the OGTT after 6 months of intervention in each group. \**P* <.05 compared with the patients with remission in the insulin group.

chronic hyperglycemia.<sup>15</sup> Although all our subjects were treated according to our accepted national guidelines during the follow-up period, glycemic control proved better in the insulin group than in the OAD group. Furthermore, we found that the average dose of antidiabetic medication administered to members of the insulin group to maintain

glycemic control was lower than that taken by the OAD group at the end of 5 years of follow-up (Table 2). This provides indirect evidence that early temporary insulin therapy may preserve  $\beta$ -cell function and/or improve insulin resistance, and consequently lead to good long-term glycemic control.



Harrison et al performed a study similar to ours to assess  $\beta$ -cell function preservation in 58 newly diagnosed T2DM patients treated either with intensive insulin therapy plus metformin or with triple oral therapy.<sup>16</sup> In their study, insulin and metformin were initiated in all patients for a 3-month lead-in treatment period. Mean A1C values substantially improved, decreasing from  $10.8\% \pm 2.6\%$  to  $5.9\% \pm 0.5\%$  in the combined treatment groups,<sup>6</sup> revealing that  $\beta$ -cell function can be preserved for at least 3.5 years by that treatment regimen. Our data showed that  $\beta$ -cell function was improved to a greater extent in the insulin group after 6 months of intervention, and remained so after 5 years of follow-up. These discrepant results could be due to differences in initial blood glucose levels (A1C 12.2% vs 10.8%) and the duration of intensive insulin therapy at diagnosis (10-14 days vs 3 months). However, when considering the results together, early intensive insulin therapy in newly diagnosed T2DM patients appears to have beneficial effects on  $\beta$ -cell function and long-term glycemic control. However, patients with higher blood glucose levels at baseline may need a longer duration of initial insulin therapy.

A number of trials have evaluated the strategy of short-term aggressive insulin therapy in patients with newly diagnosed T2DM with the goal of improving and preserving  $\beta$ -cell function and maintaining subsequent optimal glycemic control.<sup>4,8</sup> Li et al investigated the remission rate associated with transient intensive insulin therapy using continuous subcutaneous insulin infusion (CSII) in 138 newly diagnosed T2DM patients with moderate hyperglycemia.<sup>5</sup> The remission rates at months 3, 6, 12, and 24 were 72.1%, 67.0%, 47.1%, and 42.5%, respectively. Weng et al compared the effects of transient intensive insulin therapy with those of OADs on  $\beta$ -cell function and remission rates in patients with newly diagnosed T2DM with mild to moderate hyperglycemia.<sup>7</sup> The remission rate at 1 year was significantly higher in the insulin groups (51.1% in the CSII group and 44.9% in the multiple daily insulin injection group) than in the OAD group (26.7%). Taken together, these studies suggest that remission may have been due to restoration of first-phase insulin secretion. In our study, the remission rate at 5 years was significantly higher in the insulin group (27.3%) than in the OAD group (5.9%). The patients in the OAD group also initially received 10 to 14 days of intensive insulin therapy, but the remission rate in that group was low. This indicated that 10 to 14 days of intensive insulin therapy may induce short-term glycemic remission, but a subsequent 6-month course of further insulin therapy leads to long-term glycemic remission in patients with severe hyperglycemia.

## Limitations

One limitation of our study is that the sample size was relatively small. Another limitation is that we did not measure  $\beta$ -cell function and insulin resistance in the follow-up period. Therefore, we cannot directly determine the mechanisms responsible for the success of insulin therapy. A larger study is needed to confirm the beneficial effects of insulin on glycemic control, and a longer study is needed to evaluate the effects on long-term diabetic complications.

## CONCLUSIONS

Early insulin therapy in newly diagnosed T2DM patients with severe hyperglycemia is more effective than OADs in maintaining long-term glycemic control and inducing glycemic remission after 5 years. Therefore, strong consideration should be given to using early and aggressive insulin therapy for newly diagnosed Type 2 diabetic patients with severe hyperglycemia.

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## REFERENCES

- Leahy JL, Hirsch IB, Peterson KA, Schneider D. Targeting beta-cell function early in the course of therapy for type 2 diabetes mellitus. *J Clin Endocrinol Metab.* 2010;95(9):4206-4216.
- Wajchenberg BL. Beta-cell failure in diabetes and preservation by clinical treatment. *Endocr Rev.* 2007;28(2):187-218.
- Alvarsson M, Sundkvist G, Lager I, et al. Beneficial effects of insulin versus sulphonylurea on insulin secretion and metabolic control in recently diagnosed type 2 diabetic patients. *Diabetes Care.* 2003; 26(8): 2231-2237.
- Ryan EA, Imes S, Wallace C. Short-term intensive insulin therapy in newly diagnosed type 2 diabetes. *Diabetes Care.* 2004;27(5):1028-1032.
- Li Y, Xu W, Liao Z, et al. Induction of long-term glycemic control in newly diagnosed type 2 diabetic patients is associated with improvement of beta-cell function. *Diabetes Care.* 2004;27(11):2597-2602.
- Lingvay I, Legendre JL, Kaloyanova PF, Zhang S, Adams-Huet B, Raskin P. Insulin-based versus triple oral therapy for newly diagnosed type 2 diabetes: which is better? *Diabetes Care.* 2009;32(10):1789-1795.

7. Weng J, Li Y, Xu W, et al. Effect of intensive insulin therapy on beta-cell function and glycaemic control in patients with newly diagnosed type 2 diabetes: a multicentre randomised parallel-group trial. *Lancet*. 2008;371(9626):1753-1760.
8. Chen HS, Wu TE, Jap TS, Hsiao LC, Lee SH, Lin HD. Beneficial effects of insulin on glycemic control and beta-cell function in newly diagnosed type 2 diabetes with severe hyperglycemia after short-term intensive insulin therapy. *Diabetes Care*. 2008;31(10):1927-1932.
9. Nathan DM, Buse JB, Davidson MB, et al. Management of hyperglycemia in type 2 diabetes: a consensus algorithm for the initiation and adjustment of therapy: a consensus statement from the American Diabetes Association and the European Association for the Study of Diabetes. *Diabetes Care*. 2006;29(8):1963-1972.
10. Gaede P, Vedel P, Larsen N, Jensen GV, Parving HH, Pedersen O. Multifactorial intervention and cardiovascular disease in patients with type 2 diabetes. *N Engl J Med*. 2003;348(5):383-393.
11. Matsuda M, DeFronzo RA. Insulin sensitivity indices obtained from oral glucose tolerance testing: comparison with the euglycemic glucose clamp. *Diabetes Care*. 1999;22(9):1462-1470.
12. Matthews DR, Hosker JP, Rudenski AS, Naylor BA, Treacher DF, Turner RC. Homeostasis model assessment: insulin resistance and beta-cell function from fasting plasma glucose and insulin concentrations in man. *Diabetologia*. 1985; 28(7):412-419.
13. Saad MF, Knowler WC, Pettitt DJ, Nelson RG, Charles MA, Bennett PH. A two-step model for development of non-insulin-dependent diabetes. *Am J Med*. 1991;90(2):229-235.
14. Nathan DM. Clinical practice. initial management of glycemia in type 2 diabetes mellitus. *N Engl J Med*. 2002;347(17):1342-1349.
15. Samuels TA, Cohen D, Brancati FL, Coresh J, Kao WH. Delayed diagnosis of incident type 2 diabetes mellitus in the ARIC study. *Am J Manag Care*. 2006;12(12): 717-724.
16. Harrison LB, Adams-Huet B, Raskin P, Lingvay I.  $\beta$ -cell function preservation after 3.5 years of intensive diabetes therapy. *Diabetes Care*. 2012;35(7):1406-1412. ■

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■ **eAppendix.** The Study Design and CONSORT for Patient Flow Diagram

