Intensive Therapy in Newly Diagnosed Type 2 Diabetes: Results of a 6-Year Randomized Trial

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Background: This study aimed to assess the efficacy of early intensive diabetes therapy with either insulin plus metformin (INS) or triple oral therapy (TOT) with metformin, glyburide, and pioglitazone on glycemic control and A-cell function.

Methods: Fifty-eight treatment-naive newly diagnosed patients with type 2 diabetes underwent a 3-month lead-in treatment period with insulin and metformin, then were randomized to INS or TOT for 6 years. β-Cell function was measured using mixed-meal challenge test. β-Cell function remained stable throughout the 6-year study in both groups, as measured by the C-peptide area under the curve (AUC; $P = 0.13$), the AUC C-peptide/AUC glucose ($P = 0.9$), and by the disposition index ($P = 0.8$). Excellent glycemic control was maintained in both groups (end-of-study hemoglobin$_{A1c,}$ 7.3% [SD, 1.7%] INS vs 6.4% [1.4%] TOT; $P = 0.4$). There were 8 treatment failures (confirmed hemoglobin$_{A1c}$, 98%) in INS and 6 in TOT ($P = 0.93$). The predictors of treatment failure included higher fasting glucose ($P = 0.008$), fasting C-peptide ($P = 0.008$), systolic blood pressure ($P = 0.004$), and lower insulin sensitivity ($P = 0.04$) at randomization.

Conclusions: Early intensive treatment at the time of type 2 diabetes diagnosis—initial short-term insulin treatment followed by either insulin-based or intensive oral hypoglycemic–based therapy—stabilizes β-cell function for at least 6 years. Treatment failure was independent of intervention and was associated with worse disease pathology at baseline.

Key Words: β-cell function, type 2 diabetes, insulin treatment, triple oral hypoglycemic therapy, Hb_{A1c}, glycemic control, mixed-meal challenge test, insulin resistance, hypoglycemia, weight gain, quality of life

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The natural history of type 2 diabetes is hallmarked by progressive loss of β-cell function coupled with increased insulin resistance. This is thought to be due to the combined toxic effects of hyperglycemia and increased free fatty acids (glucolipotoxicity).[1] The shorter and less severe the glucolipotoxicity insulin, the more β-cell preservation and/or recovery can be expected. A higher β-cell function has been associated with improved glycemic control, less treatment burden, and fewer microvascular complications.[2] We hypothesize that early and intensive antihyperglycemic therapy may change the natural course of the disease by preserving β-cell function.

The Outcome Reduction With Initial Glargine Intervention Trial explored whether the early use of insulin glargine, compared with standard-of-care treatment, in patients with impaired fasting glucose, impaired glucose tolerance, or newly diagnosed type 2 diabetes[3] can prevent disease progression. In the 1456 patients without diabetes, those who were assigned to insulin glargine were 28% less likely to develop diabetes during the 6.2 years of follow-up, an effect presumed to be due to stabilization/improvement in β-cell function. Although this approach did not show an overall decrease in cardiovascular events during the study follow-up, a proactive treatment approach, very early in the course of the disease, could have longer term impact on the disease course and thus be superior to the current reactive approach where treatment is only initiated or escalated as the disease worsens.

Short-term (2–3 weeks) intensive insulin treatment has been shown to result in disease remission in some patients, especially those with newly diagnosed diabetes.[4–6] Unfortunately, this approach alone, without subsequent treatment, is not durable because more than 50% of patients required additional treatment by 1 year. Weng et al.[7] compared a short course of oral therapy with insulin therapy in patients with newly diagnosed type 2 diabetes. After normogycemia was attained, the treatment was discontinued and the patients were observed for 1 year. Fewer patients reached control (83.5% vs 95%–97%) or attained remission at 1 year (26.7% vs 45%–50%) in the oral group,[7] suggesting that initial insulin treatment may have a stronger β-cell preservation effect, yet still not sufficient to change the course of the disease long-term in the absence of subsequent therapy. Therefore, short-term intensive treatment, whether with insulin or oral hypoglycemic agents, in the absence of subsequent maintenance treatment is not sufficient to preserve β-cell function long-term. Chen et al.[8] performed a study where both groups received initial insulin therapy followed by randomized to oral therapy or insulin. The insulin group preserved more β-cell function at 6 months, but it is unclear if this was due to the treatment received or the glycemic targets achieved (the oral group had significantly higher Hb_{A1c} throughout the study).[8]

Long-term studies in patients with newly diagnosed diabetes evaluated diet therapy and monotherapy with metformin, sulfonylureas, or glitazones, but none of these monotherapy

interventions were successful in stabilizing the disease process[9,10] beyond the initial 6 to 18 months. There are no long-term studies to investigate whether insulin is superior to an intensive oral therapy in preserving β-cell function, especially when similar glycemic control is maintained between groups.

We evaluated whether short-term (3 months) insulin therapy followed by either continued insulin regimen or a multidrug oral regimen can achieve and maintain long-term (6 years) glycemic control and preserve β-cell function. Safety and quality-of-life parameters were also compared.

RESEARCH DESIGN AND METHODS

We recruited newly diagnosed treatment-naive patients with type 2 diabetes from Parkland Memorial Hospital inpatient and outpatient services and accepted self-referrals to the University of Texas Southwestern (UTSW) Clinical Diabetes Research Clinic. The study was approved by the UTSW Institutional Review Board, and all patients signed informed consent (clinical trials registration number NCT00232583).

Patients were treated with insulin and metformin for 3 months and then randomized to treatment with insulin plus metformin (INS) or triple oral therapy (TOT) with metformin, pioglitazone, and glyburide. The results from the first 3-month run-in period, the glycemic control and quality of life at 3 years, and the β-cell function at 3.5 years were published previously.[11–13] The current article describes the final study results after 6 years of follow-up, including β-cell function, glycemic control, safety parameters, quality of life, and analysis of the treatment failure predictors.

Participants/Eligibility

Eligible patients were 21 to 70 years old, were diagnosed with type 2 diabetes in the previous 2 months, and were treatment-naive. Exclusion criteria were published previously and are notable for type 1 diabetes–related antibodies and baseline Hb_{A1c} level of less than 7%.[11]

Randomization/Interventions

All participants were initiated on insulin and metformin for a 3-month lead-in period to attain similar glycemic control and reverse any temporary β-cell stunning due to glucotoxicity by the time of randomization. NovoLog mix 70/30 by Flexpen and metformin were initiated and titrated based on a previously published algorithm.[12] At the end of 3 months, patients were assigned (via blocked randomization stratified by African American race and body mass index [BMI]) to continue the same insulin-based therapy (INS group) or switch to TOT (TOT group) with metformin (1000 mg twice daily), glyburide, and pioglitazone (45 mg daily) as described previously.[13] Insulin and glyburide were titrated throughout the study based on home capillary glucose levels, targeting a fasting glucose level of less than 100 mg/dL and a predinner value of less than 140 mg/dL.

Patients were observed at the Clinical Diabetes Research Center at UTSW monthly initially and then quarterly for a total of 72 months. Treatment failure was a predefined study end point defined as Hb_{A1c} of more than 8% confirmed by a second reading and occurring after maximization of the glyburide dose or adequate insulin dose titration. A treatment failure in the TOT group would prompt a group switch (from TOT to INS), whereas a treatment failure in the INS group would lead to intensification of the insulin regimen (3–4 injections per day). Follow-up after treatment failure continued as scheduled, and all analyses were performed according to the original assigned group (intention to treat) even after treatment failure.

Measurements

Glycemic control was evaluated by Hb_{A1c} (high-performance liquid chromatography at the Clinical Diabetes Laboratory at UTSW) every 3 months. Lipid profile, alanine aminotransferase, aspartate aminotransferase, creatinine, hemoglobin, high-sensitivity C-reactive protein (hsCRP), plasminogen activator inhibitor 1 (PAI-1), and fibrinogen were measured twice a year in a commercial laboratory (Quest Diagnostics, Irving, TX). The evaluation of β-cell function via mixed-meal challenge testing (MMCT) was performed, using high-protein boost concentrate of 1 g/kg carbohydrate equivalent, at 0, 6, 12, 18, 30, 42, 54, and 72 months postrandomization. Patients fasted for 12 hours before the test, and all antidiabetic agents were withheld for 24 hours before each testing. Glucose and C-peptide were measured at baseline (before the ingestion of the mixed meal) and then 7 times over the 3-hour test (15, 30, 60, 90, 120, 150, and 180 minutes). Glucose was measured using a Yellow Springs Instrument (Yellow Springs, CA), whereas C-peptide was measured using Radioimmunoassay (Millipore, Billerica, MA) in the Clinical Diabetes Laboratory at UTSW. Unfortunately, the C-peptide specimens from the final (72-month) visit were compromised because of storage failure; therefore, these data are missing.

Insulin secretion was estimated using the area under the curve (AUC) for glucose (G) and C-peptide (C) (total, incremental, 0–30 minutes, and 0-maximal production) and then determining ratios (C/G) to estimate insulin production. Insulin sensitivity was calculated using the C-peptide–based Matsuda index.[14,15] We used C-peptide instead of insulin levels to eliminate cross-contamination with exogenous insulin and insulin antibodies. The calculation was done according to the following formula:

$$\text{Matsuda index} = \frac{500,000}{\sqrt{[(C_O \times G_O \times 333) \times (C\mathit{mean} \times G\mathit{mean} \times 333)]}}$$

The disposition index (DI) was measured by multiplying the insulin secretion (AUC_C/AUC_G) by the Matsuda index.[16] The DI reflects the β-cell function adjusted for total body insulin sensitivity.

Compliance was estimated by medication inventory at each encounter. Weight was measured on the same scale at every visit. Mild hypoglycemic events (symptoms of low blood glucose accompanied by a documented capillary blood glucose value of <70 mg/dL) and severe hypoglycemic events (symptoms of hypoglycemia that required assistance from another individual for treatment, regardless of capillary blood glucose level) were recorded at each visit. Glucose strips were provided to all patients, and they were asked to check at least 2 times daily throughout the study.

Quality of life was measured using the modified Diabetes Quality of Life Clinical Trial Questionnaire at randomization, 6, 18, 42, and 72 months. The details and rational for choosing this assessment tool were described previously.[13]

Statistical Analysis

The original sample size was estimated to detect differences between the INS and TOT groups in the primary outcome of the study, the C-peptide AUC of 240 ng/mL per minute with an estimated SD of 225 ng/mL per minute. To detect this effect size, 20 patients in each group was needed for power of 90% at $\alpha = 0.05$.

The intention-to-treat analysis is reported, which included all subjects according to their randomization treatment assignment,

including those who reached the predefined treatment failure end point and were switched from TOT to INS.

The AUC from the MMCT was computed using the trapezoidal rule. Biochemical measurements, AUC, DI, and insulin sensitivity responses were assessed with mixed linear model repeated measures analysis. Continuous variables that were positively skewed were log transformed before analysis. The measurements obtained throughout the 72 months (54 months for C-peptide–derived variables) of treatment were included in the analysis. The primary repeated measures models consisted of a treatment group factor, study time (month) factor, and interaction between group and time, with subject modeled as a random effect. Between- and within-group contrasts were constructed from these models, and the difference in response between treatment groups was assessed via an interaction effect. Hypoglycemic event rates were analyzed with Poisson repeated-measures models. To assess the longitudinal changes in subjects who reached the treatment failure end point, the mixed-model analysis that was further stratified by treatment failure status and interactions between treatment, failure, and time were assessed. A comparison of treatment failure rates was made with the log-rank test. Cox proportional hazards regression models were used to compare characteristics by treatment failure status of the 2 treatment regimens to account for varying failure times and estimate hazard ratios for prediction of treatment failure. Results are presented as mean and SD, unless otherwise specified. A 2-sided P value of less than 0.05 was considered statistically significant. Statistical analysis was performed with SAS version 9.3 (SAS Institute, Cary, NC).

RESULTS

Sixty-three patients were enrolled in the study from November 2003 to June 2005, and 58 patients completed the 3-month run-in period; 29 patients were randomized to continue INS and 29 patients were changed to TOT (Fig. 1). The baseline characteristics of the entire population were 36% females, more than 80% minorities (43% African American, 38% Hispanic), 44.9 (SD, 10.1) years old, and were similar between the 2 groups (Table 1). The completion rates at 6 years in the study were 19 (66%) of the 29 patients in the INS group and 16 (55%) of the 29 patients in the TOT group (see Fig. 1 for description of dropouts in each group).

Glycemic Control

During the initial 3-month lead-in period, Hb_{A1c} was substantially improved from 10.8% (SD, 2.6%) to 5.9% (SD, 0.5%; $P < 0.0001$),[12] and 100% of patients had a Hb_{A1c} of 7% or less. The Hb_{A1c} at the final visit in the study was 7.3% (SD, 1.7%; median, 6.5%) in INS and 6.4% (SD, 1.4%; median, 5.9%) in TOT (interaction, $P = 0.42$; Fig. 2A and Table 1). At 6 years,

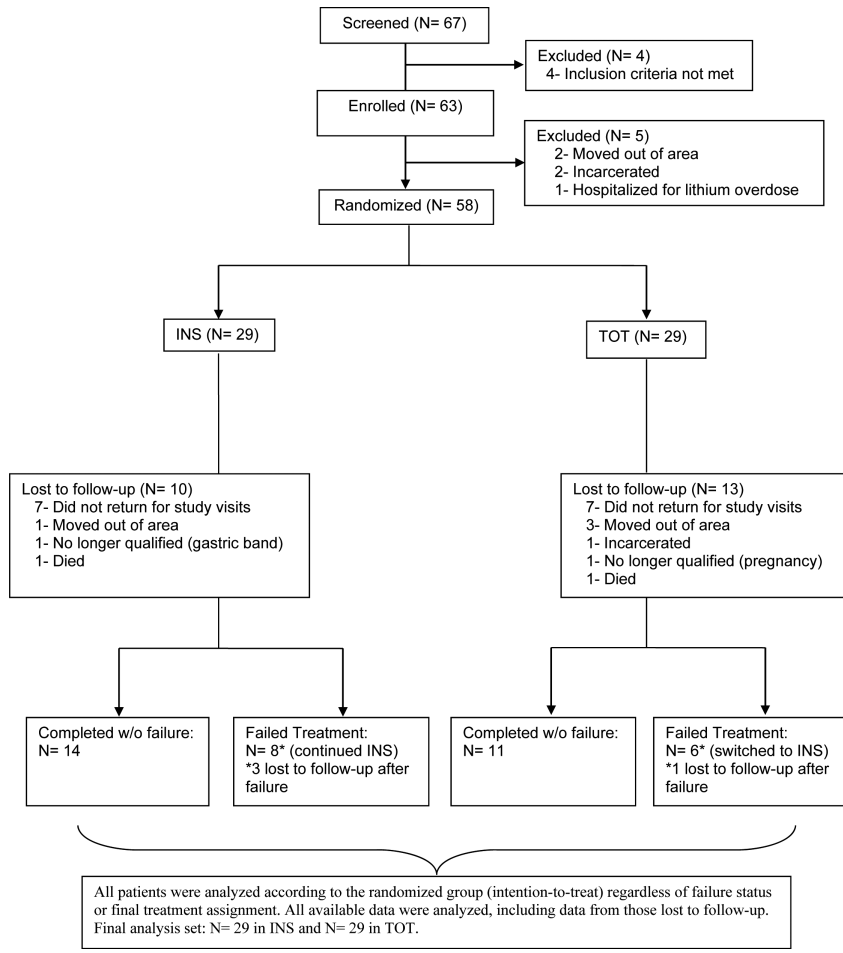

FIGURE 1. Participant flow chart. INS indicates insulin group (treated with insulin plus metformin); TOT, TOT group (treated with metformin plus glyburide plus pioglitazone); w/o, without.

TABLE 1. Demographic and Biochemical Characteristics at Randomization and Final Visit in the Study

	Randomization		Final Visit	
	INS (n = 29)	TOT (n = 29)	INS (n = 29)	TOT (n = 29)
Age, y	44.8 (9.7)	45.0 (10.7)	—	—
Sex (male/female)	20/9	17/12	—	—
Ethnicity (AA/H/W/O), %	41/38/21/0	45/38/14/3	—	—
Compliance, %*	90.5 (14.1)	95.3 (9.5)	89 (19.4)	86.1 (15.5)‡
Weight, kg	102.2 (24.9)	100.9 (23.0)	107.7 (31.3)†	107.9 (31.4)‡
BMI, kg/m^2	35.6 (6.6)	36.5 (8.0)	37.5 (9.2)†	39 (10.8)‡
Hb_{A1c}, %	6.0 (0.5)	5.9 (0.5)	7.3 (1.7)†	6.4 (1.4)‡
Insulin dose, U/kg	0.63 (0.29)	0.59 (0.21)	0.92 (0.55)†	NA
Mild hypoglycemia, events per month	1.2 (2.5)	1.2 (1.5)	0.5 (1.0)†	0.5 (0.9)‡
Total cholesterol, mg/dL	169.6 (38.5)	171.2 (32.4)	163 (36.5)	184.1 (55)
Low-density lipoprotein, mg/dL	96.9 (33.7)	101.6 (29.8)	87.2 (34.1)	98.6 (35.6)
High-density lipoprotein, mg/dL	41.3 (9.6)	42.3 (10.8)	46.7 (15.7)†	45.3 (9.7)
Triglycerides, mg/dL	120 (97)	112 (65)	128 (78)	127 (88)
Lipid medication, %	34.5	17.2	79.3	75.9
Systolic blood pressure, mm Hg	125.6 (15.8)	122.5 (13.6)	128 (19.5)	125.9 (16.9)
Diastolic blood pressure, mm Hg	76.7 (10.4)	78.3 (9.7)	78 (14.5)	75.9 (9.1)‡
Number of blood pressure medications	1.0 (1.3)	0.7 (0.9)	1.8 (1.5)	1.5 (1.3)
Creatinine, mg/dL	0.92 (0.23)	0.91 (0.24)	0.89 (0.21)	0.98 (0.52)
Hemoglobin, g/dL	14.0 (1.3)	14.2 (1.8)	14.1 (1.3)	13.7 (2.0)
ALT, U/L*	21.8 (9.0)	21.0 (10.1)	33.8 (28.9)†	17.4 (9.9)
AST, U/L	19.0 (8.3)	18.8 (9.5)	29.3 (28.4)†	17.2 (5.2)
hsCRP, mg/L	6.3 (8.8)	6.9 (7.7)	5.4 (8.2)	6.1 (8.9)
Fibrinogen, mg/dL	384.0 (80.2)	399.0 (82.6)	350.6 (75.2)	395.4 (98.5)
PAI-1, IU/L	18.8 (14.8)	13.9 (11.7)	20 (15.1)	16.7 (18)
MMCT				
Fasting glucose, mg/dL	111.6 (24.7)	101.8 (19.1)	154.7 (84.9)†	118.7 (59.9)
Fasting insulin, μIU/mL*	19.4 (17.2)	22.8 (22.0)	27.3 (20.9)	14.5 (21.0)‡
AUC_G, mg/dL per minute	29723 (6297)	29819 (6905)	32596 (8411)	30414 (14119)
AUC_C , ng/mL per minute	1624 (576)	1646 (663)	2096 (795)†	1725 (618)
Ratio (AUC_C/AUC_G)	0.058 (0.025)	0.057 (0.028)	0.066 (0.025)	0.066 (0.029)
$\Delta G_{30\text{-}0\ minutes}$, mg/dL	46.0 (20.0)	54.3 (30.5)	47.6 (17.6)	48.3 (26.3)
$\Delta C_{30\text{-}0\ minutes}$, ng/mL*	2.8 (2.4)	4.1 (3.3)	4.9 (3.1)†	4.0 (3.3)
Ratio $(\Delta C/\Delta G)_{30\text{-}0\ minutes}$	0.070 (0.061)	0.080 (0.067)	0.125 (0.132)†	0.112 (0.108)
G max, mg/dL	195.5 (37.8)	198.8 (50.1)	211.3 (50.6)	200.6 (91.1)
C max, ng/mL*	12.1 (4.7)	12.1 (5.1)	15.7 (6.7)†	12.5 (4.3)
$\Delta G_{0\text{-}max}$, mg/dL	83.8 (26.8)	92.6 (35.2)	88.4 (33.9)	84.0 (48.3)
$\Delta C_{0\text{-}max}$, ng/mL*	8.8 (4.1)	9.1 (4.9)	11.0 (6.1)†	8.8 (2.9)
Ratio $(\Delta C/\Delta G)_{0\text{-}max}$	0.116 (0.067)	0.105 (0.060)	0.142 (0.085)	0.173 (0.193)‡
Matsuda index	2.73 (1.40)	3.12 (2.62)	2.11 (1.47)†	2.45 (1.09)‡
DI (AUC_C/AUC_G)	0.15 (0.07)	0.16 (0.09)	0.12 (0.07)	0.16 (0.09)

Data are mean (SD).

*Interaction factor (group × time) from repeated measures analysis of all measurements from randomization to year 6 ($P < 0.05$).

†Change in the INS group over time ($P < 0.05$).

‡Change in the TOT group over time ($P < 0.05$).

AA indicates African American; ALT, alanine aminotransferase; AST, aspartate aminotransferase; C, C-peptide; G, glucose; H, Hispanic; INS, insulin group; max, maximum; O, other; TOT, triple oral therapy group; W, white.

63.2% in the INS group and 68.8% in the TOT group ($P = 0.73$) met the American Diabetes Association target of Hb_{A1c} of less than 7%, and the average frequency of Hb_{A1c} of less than 7% over the entire study was 83.9% for INS and 85.5% for TOT. The total daily dose of insulin increased from 0.63 (SD, 0.29) U/kg per day at randomization to a final visit dose of 0.92 (SD, 0.55) U/kg per day in INS ($P = 0.008$ within INS group).

β-Cell Function and Insulin Sensitivity

β-Cell function remained stable over time in both groups, as measured by AUC_C (primary outcome of the study, $P = 0.13$), AUC_C/AUC_G ($P = 0.9$), and DI ($P = 0.8$; Figs. 2D, F and Table 1), with no between-group differences. Insulin sensitivity (Matsuda index) decreased comparably in both groups over time ($P = 0.0006$ in INS and $P = 0.02$ in TOT; Fig. 2E and Table 1). The

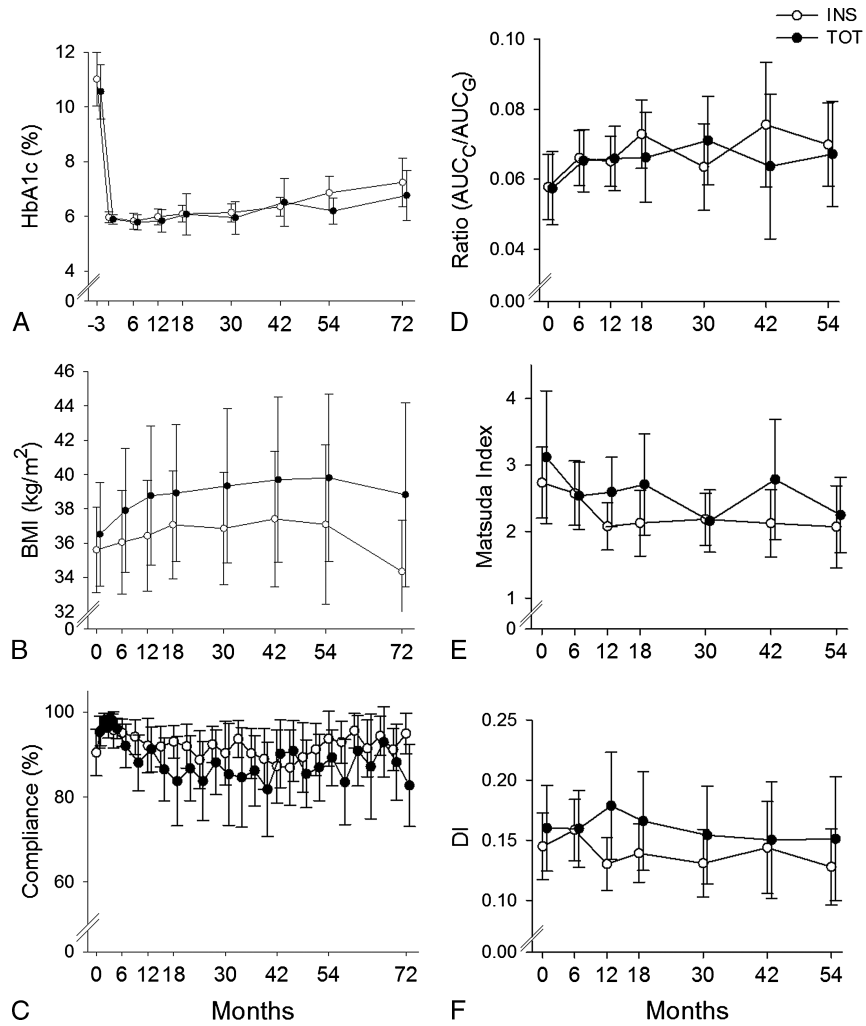

FIGURE 2. Major study outcomes by treatment group, as measured over the 6-year study follow-up. A, Hb_{A1c}. B, Body mass index. C, Treatment compliance. D, AUC_C/AUC_G from MMCT. E, Matsuda index (measure of insulin sensitivity) derived from MMCT. F, Disposition index from MMCT.

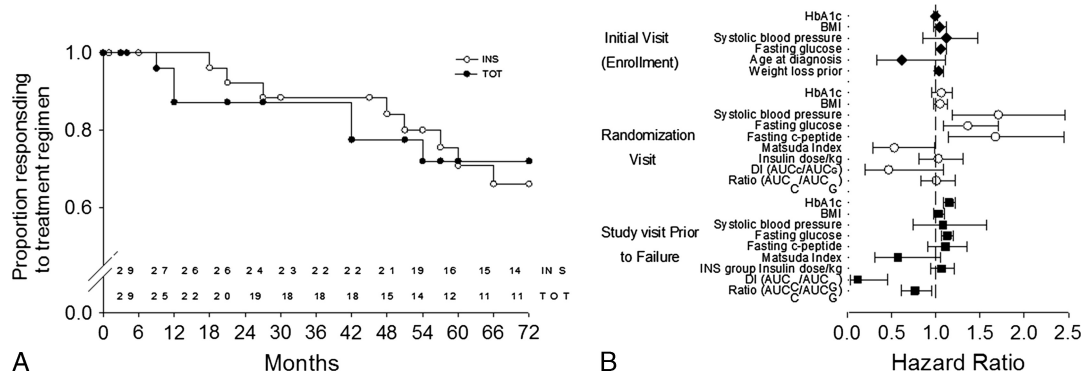

FIGURE 3. Assessment of treatment failure over the 6-year study period in the INS and TOT groups. A, Kaplan-Meier curve depicting time of treatment regimen failure by group. The numbers represent the number of patients at risk at each time point by treatment group. B, Hazard ratios from Cox proportional hazards models for prediction of treatment failure. Hazard ratios represent per 1 unit change in the predictor variable except for age, fasting glucose, and systolic blood pressure (per 10 unit change), Hb_{A1c} and DI (per 0.1 unit change), and AUC_C/AUC_G ratio (per 0.01 unit change).

TABLE 2. Study Participant Characteristics by Treatment Regimen and Failure Status at Initial Visit, Randomization Visit, Visit Before Failure, and Last Visit in the Study

	INS Regimen		TOT Regimen		
	Non Failure (n = 21)	Failure (n = 8)	Non Failure (n = 23)	Failure (n = 6)	*P** Nonfailure vs Failure
Initial visit (enrollment)					
Age at diagnosis, y	45.9 (10.1)	41.8 (8.4)	45.0 (11.3)	45.2 (8.8)	0.11
Sex (male/female)	13/8	7/1	13/10	4/2	0.35
Ethnicity (AA/H/W/O), %	43/33/24/0	37.5/50/12.5/0	52/35/9/4	17/50/33/0	0.25
BMI, kg/m^2	34.8 (4.1)	36.5 (10.4)	36.0 (8.1)	36.8 (9.3)	0.25
Weight loss prior, kg	7.6 (8.5)	7.1 (7.5)	5.2 (6.2)	13.2 (16.4)	0.18
SBP, mm Hg	125.4 (18.1)	119.9 (23.4)	120.6 (16.9)	132.3 (27.9)	0.42
Hb_{A1c}, %	11.1 (2.7)	10.9 (2.2)	10.6 (2.5)	10.5 (3.3)	0.72
Fasting glucose, mg/dL	152.1 (69.2)	142.9 (79.2)	127.8 (49.9)	227.7 (128.5)	0.07
hsCRP, mg/L	8.4 (9.9)	5.2 (7.0)	10.2 (15.5)	12.9 (12.2)	0.94
Randomization visit					
Insulin dose, U/kg	0.65 (0.32)	0.59 (0.19)	0.60 (0.19)	0.55 (0.28)	0.82
Treatment compliance, %	92.6 (12.5)	85.1 (17.3)	95.3 (10.0)	95.0 (8.5)	0.11
SBP, mm Hg	122.1 (14.0)	134.6 (17.6)	120.2 (11.0)	131.0 (19.4)	0.004
Hb_{A1c}, %	5.9 (0.5)	6.2 (0.5)	5.9 (0.5)	5.9 (0.5)	0.30
Fasting glucose, mg/dL	109.0 (24.2)	118.4 (26.6)	97.0 (15.0)	120.0 (23.6)	0.008
Fasting C-peptide, ng/mL	3.0 (1.5)	4.3 (1.6)	2.8 (1.1)	3.5 (1.1)	0.008
Matsuda index	2.95 (1.48)	2.17 (1.04)	3.37 (2.87)	2.15 (0.85)	0.04
Ratio $(\Delta C/\Delta G)_{30\text{-}0\ minutes}$	0.074 (0.061)	0.060 (0.066)	0.093 (0.067)	0.029 (0.034)	0.07
Ratio (AUC_C/AUC_G)	0.054 (0.023)	0.067 (0.028)	0.061 (0.028)	0.045 (0.022)	0.95
DI (AUC_C/AUC_G)	0.15 (0.08)	0.14 (0.06)	0.18 (0.09)	0.10 (0.08)	0.08
Study visit before failure					
Insulin dose, U/kg	0.8 (0.5)	0.9 (0.2)			0.30
Treatment compliance, %	85.5 (21.6)	90.6 (13.7)	87.9 (21.3)	72.0 (25.7)	0.33
SBP, mm Hg	129.6 (14.9)	121.1 (12.9)	123.0 (14.1)	135.7 (15.1)	0.68
Hb_{A1c}, %	6.3 (0.6)	8.3 (0.5)	5.9 (0.7)	7.9 (1.0)	<0.0001
Fasting glucose, mg/dL	121.1 (39.1)	157.6 (65.3)	97.9 (21.0)	248.0 (107.5)	<0.0001
Fasting C-peptide, ng/mL	4.6 (2.7)	4.8 (3.1)	3.8 (1.7)	5.4 (2.5)	0.31
Matsuda index	2.25 (1.31)	1.99 (1.26)	2.61 (1.12)	1.39 (0.69)	0.08
Ratio $(\Delta C/\Delta G)_{30\text{-}0\ minutes}$	0.141 (0.145)	0.059 (0.034)	0.125 (0.114)	0.074 (0.044)	0.11
Ratio (AUC_C/AUC_G)	0.076 (0.027)	0.052 (0.017)	0.073 (0.026)	0.054 (0.036)	0.02
DI (AUC_C/AUC_G)	0.15 (0.06)	0.10 (0.07)	0.18 (0.08)	0.06 (0.04)	0.002
At final visit					*P*† Failure as Main Effect
BMI, kg/m^2	36.0 (5.3)	41.4 (15.3)	38.7 (11.1)	40.2 (10.4)	0.19
Insulin dose, U/kg	0.8 (0.5)	1.3 (0.3)	NA	1.6 (1.0)	0.007
Hb_{A1c}, %	6.5 (1.3)	9.2 (1.2)	5.9 (0.6)	8.2 (1.9)	<0.0001
Fasting glucose, mg/dL	142.7 (92.2)	186.3 (54.4)	101.5 (23.9)	184.5 (104.8)	0.0003
Fasting C-peptide, ng/mL	4.7 (2.7)	4.7 (3.0)	3.6 (1.6)	4.1 (3.6)	0.78
Matsuda index	2.13 (1.31)	2.05 (1.91)	2.67 (1.11)	1.61 (0.47)	0.05
Ratio $(\Delta C/\Delta G)_{0\text{-}30\ minutes}$	0.143 (0.143)	0.076 (0.068)	0.125 (0.114)	0.049 (0.040)	0.07
Ratio (AUC_C/AUC_G)	0.075 (0.023)	0.048 (0.023)	0.071 (0.025)	0.037 (0.031)	0.0006
DI (AUC_C/AUC_G)	0.14 (0.06)	0.08 (0.07)	0.18 (0.08)	0.05 (0.02)	<0.0001

All values reported as mean (SD).

**P* values are from Cox regression models to account for varying failure times.

†*P* values are for mixed-model repeated measures with failure as main effect.

AA indicates African American; C, C-peptide; G, glucose; H, Hispanic; I, incremental; O, other; W, white.

baseline-to-30-minute ($P = 0.006$) and baseline-maximum ($P = 0.02$) C-peptide responses during MMCT increased significantly more over time in the INS group compared with the TOT group. There was no difference between groups in glucose total AUC, 0 to 30 minutes, 0-maximal production, or ratio of C-peptide to glucose (total AUC, 0–30, or 0-maximal production; Table 1).

Fasting insulin levels decreased throughout the study in TOT whereas remaining stable in INS ($P = 0.0002$), yet the relevance of this measurement in the insulin-treated group is very limited.

Treatment Failure

Treatment failure occurred in 8 (27.6%) patients in the INS group and 6 (20.7%) patients in the TOT group (log-rank, $P = 0.93$) at an average of 43.1 (SD, 18.4) months and 29.5 (SD, 18.8) months, respectively (Fig. 3A). The predictors of treatment failure at the time of randomization included a higher systolic blood pressure ($P = 0.004$), fasting C-peptide ($P = 0.008$), fasting glucose ($P = 0.008$), and a lower insulin sensitivity ($P = 0.04$; Table 2 and Fig. 3B). At the visit before failure, those who failed had a higher fasting glucose ($P = <0.0001$) and a lower AUC_C/AUC_G ($P = 0.02$) and DI ($P = 0.002$; Fig. 3B). At the final visit in the study, the group who failed had significantly higher insulin doses ($P = 0.007$), Hb_{A1c} ($P = <0.0001$), and lower AUC_C/AUC_G ($P = 0.0006$) and DI ($P < 0.0001$). No other significant predictors were identified at the initial visit, randomization, or visit before failure, including treatment assignment, race, age, BMI, weight loss before diagnosis, initial insulin dose, medication compliance, inflammatory markers, and other MMCT variables not mentioned previously (Table 2).

The Hb_{A1c} at the time of failure was 9.4% (SD, 1.8%) in INS and 9.5% (SD, 2.1%) in TOT. The average Hb_{A1c} in the failure group did not improve with increasing doses of insulin in INS (final visit Hb_{A1c}, 9.1% [SD, 1.2%]) and improved but did not reach the goal after change to insulin treatment in TOT (final visit Hb_{A1c}, 8.2% [SD, 1.9%]; Figs. 4A, B). Insulin sensitivity (Matsuda index) was not different between those who failed and those who did not in INS ($P = 0.37$) but was lower in the TOT failures ($P = 0.0004$; Figs. 4E, F); thus, failures in the TOT group seem to be the nonresponders to the insulin-sensitizing effect of this regimen. Absolute insulin

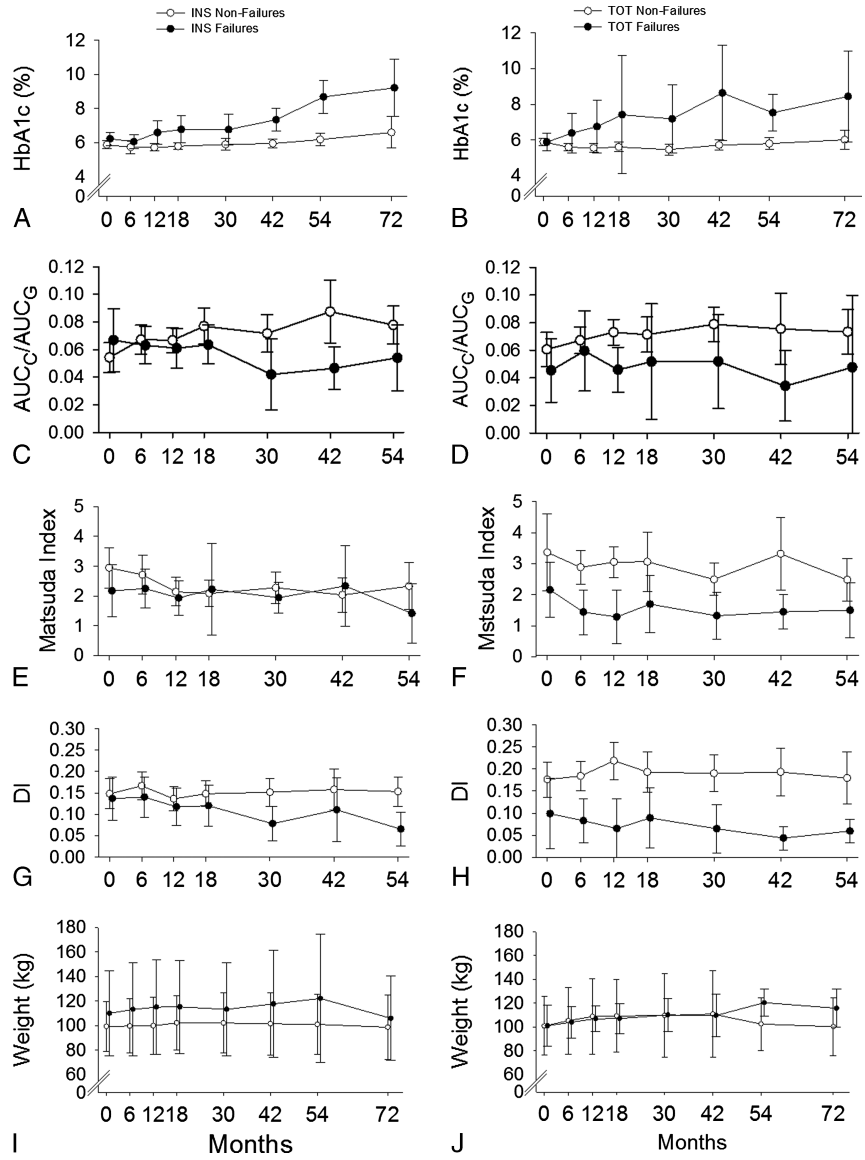

FIGURE 4. Comparison of the changes in Hb_{A1c}, AUCc/AUC_G, Matsuda index, DI, and weight over time in the INS group (A, C, E, G, I) and the TOT group (B, D, F, H, J) by failure status.

production (AUC_C/AUC_G) and β-cell function (DI) declined faster over the course of the study in those who failed versus those who did not fail treatment in both INS ($P = 0.01$) and TOT ($P < 0.0001$; Figs. 4C, D, G, H), despite similar baseline values. Weight did not significantly differ by failure status in either group (Figs. 4I, J).

At the final visit in the study, the total daily dose of insulin in the INS treatment failures was 1.3 (SD, 0.3) U/kg per day

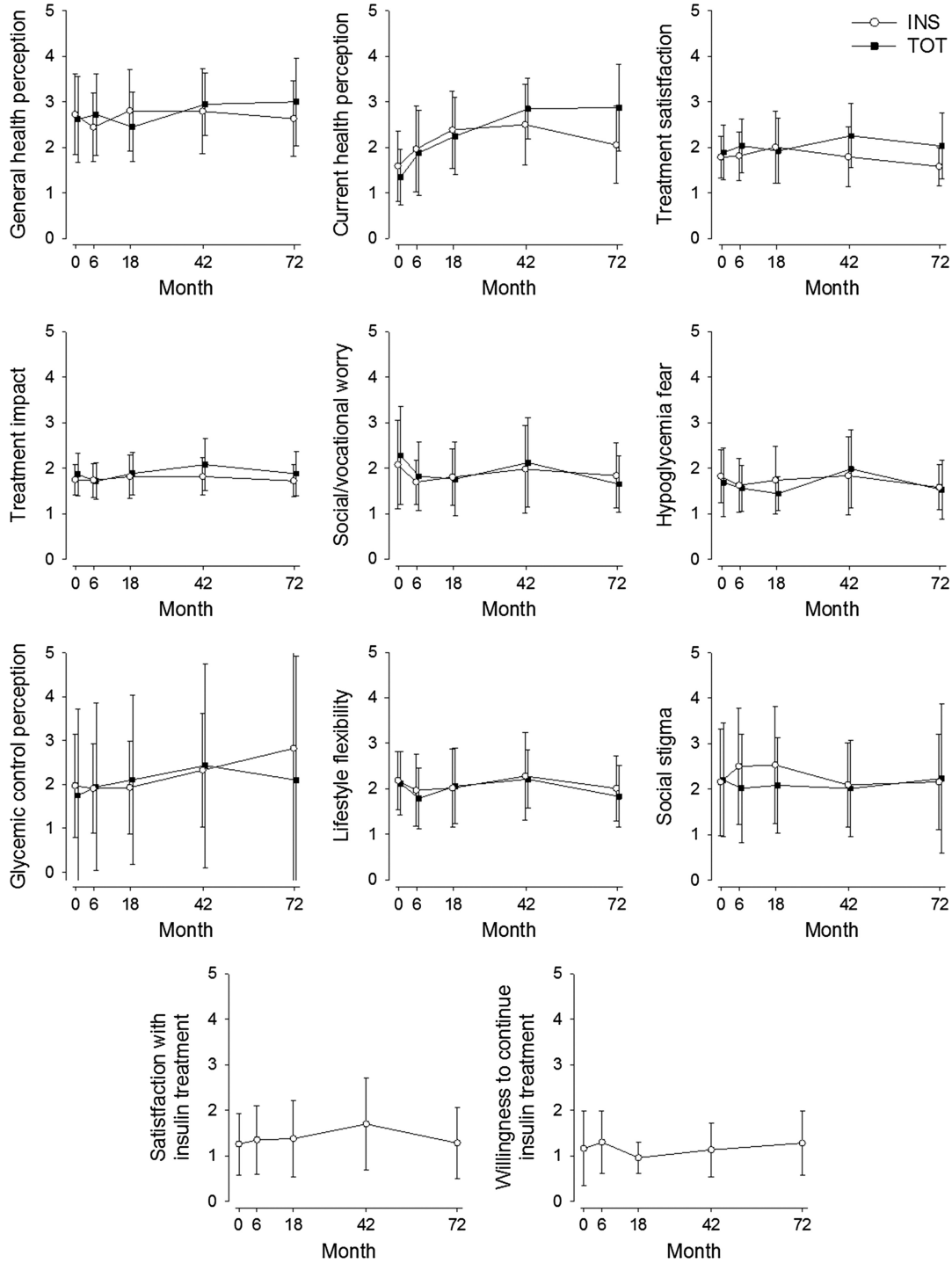

FIGURE 5. Results of modified Diabetes Quality of Life Questionnaire in the INS and TOT groups. All patients were given the questionnaire to complete at randomization and at 6, 18, 42, and 72 months after randomization. Patients randomly assigned to TOT did not complete the 2 questions regarding insulin. The results are reported as means (SD) of the Likert scale score of 1 to 5. Both groups had similar responses at month 72 except for current health perception, which was better at month 72 in the INS group compared with the TOT group (group × month 72 interaction, $P = 0.002$).

(n = 8), whereas the total daily dose of insulin in the TOT treatment failures was 1.6 (SD, 1.0) U/kg per day (n = 6), both doses being much higher than the average insulin dose at the same time point in the entire cohort (0.9 U/kg).

Safety

Most subjects (76%) were obese at randomization, with an overall average BMI of 36.1 (SD, 7.3) kg/m^2. Over the 6 years of follow-up, BMI increased significantly and comparably in both groups ($P = 0.04$ in INS and $P = 0.01$ in TOT, $P = 0.48$ between groups; Fig. 2B and Table 1).

Alanine aminotransferase increased significantly in INS ($P = 0.007$ between groups). Hemoglobin and creatinine did not differ significantly between study groups (Table 1).

There was an overall low rate of mild hypoglycemia. The rate of hypoglycemia (defined conservatively as a documented capillary blood glucose level of less than 70 mg/dL in the presence of symptoms suggestive of hypoglycemia) decreased rapidly over the first 6 months into the study and remained low thereafter in both groups (from 1.2 [SD, 2.5] to 0.5 [1.0] events per month in INS [$P = 0.002$] and from 1.2 [1.5] to 0.5 [0.9] events per month in TOT [$P = 0.006$]), with no difference between groups over time (Table 1). Severe hypoglycemia was rare, with 3 patients in the INS group having 4 events (3 within the first month postrandomization) and 4 patients in the TOT group having 7 events (4 within the first 2 months postrandomization).

Compliance and Quality of Life

The overall compliance with medications throughout the study was 92.8% (SD, 9.1%) in INS and 89.6% (SD, 10.3%) in TOT ($P = 0.33$; Fig. 2C). Compliance rate was more than 80% in 85.4% of INS and 74.0% of TOT participants. Compliance rate decreased significantly over the course of 6 years in TOT ($P = 0.005$), whereas it remained stable in INS ($P = 0.63$).

All 12 domains of the quality of life survey were similar between groups and stable over time, except for current health perceptions which improved more in INS ($P = 0.002$). Satisfaction with insulin treatment and willingness to continue insulin injections were both very high (1.4 [SD, 0.7] and 1.1 [0.4], respectively, on a 1–5 scale where "1 is extremely satisfied, extremely willing") and stable in the INS group throughout the 6 years (Fig. 5).

Cardiovascular Risk Markers

There was no significant change over time or between groups in total cholesterol, LDL, or triglycerides (Table 1). HDL increased significantly more in INS ($P = 0.002$), although it was not different between groups ($P = 0.22$). Statin use increased over the study period from 34.5% to 79.3% in the INS group and from 17.2% to 75.9% in the TOT group.

Systolic blood pressure did not change over time in either group. Diastolic blood pressure decreased over time in the TOT group ($P = 0.02$) but was not significantly different from the INS group ($P = 0.3$). The number of blood pressure medications increased from 1.0 (SD, 1.3) to 1.8 (SD, 1.5) in the INS group and from 0.7 (SD, 0.9) to 1.5 (SD, 1.3) in the TOT group (Table 1).

There were no significant changes in hsCRP, fibrinogen, or PAI-1 between groups or over time (Table 1).

CONCLUSIONS

β-cell function, as measured by C-peptide secretion (AUC_C and AUC_C/AUC_G) and by DI, as well as good glycemic control were maintained for 6 years in patients with newly diagnosed type 2 diabetes. These results were observed regardless of randomization to treatment with insulin and metformin or a triple oral hypoglycemic regimen with metformin, glyburide, and pioglitazone, both regimens instituted after an initial 3-month run-in period with insulin and metformin. Insulin sensitivity, measured by the Matsuda index, decreased in both groups over the course of the study. Overall, these findings suggest that early intervention in the course of the disease, with an intensive regimen that has complementary mechanisms of action, can stabilize the course of the disease and preserve the progressive decline in β-cell function well known to occur in this patient population.

Despite the overall β-cell preservation in both groups, nearly 24% of the cohort experienced treatment failure even in the setting of early and intensive treatment. Because the study was designed to compare 2 intensive treatment interventions and it did not have a conventionally treated control group (using the traditional stepwise treatment algorithm), it is not possible to conclude whether intensive treatment improves failure rate over the traditional stepwise treatment algorithm. Furthermore, we cannot compare the failure rate across different studies because failure criteria vary widely, as is the length of follow-up and the study population. The Diabetes Outcome Progression Trial (ADOPT) study compared 3 different monotherapy agents in newly diagnosed patients with type 2 diabetes.[9] The reported failure rates at 5 years of treatment were 15% with rosiglitazone, 21% with metformin, and 34% with glyburide monotherapy. Although these failure rates seem comparable with those seen in our study, the failure definition used in ADOPT study was more conservative than ours, defined as fasting plasma glucose of above 180 mg/dL on 2 occasions. In addition, all treatment groups in this study experienced a gradual decline in β-cell function, whereas we observed a stable β-cell function throughout our follow-up. The Treatment Options for Type 2 Diabetes in Adolescents and Youth (TODAY) study, which enrolled children with type 2 diabetes (average age, 14.0 [SD, 2.0] years[17]), defined treatment failure the same as our study (Hb_{A1c}, >8%). This end point was achieved by 51.7% of patients treated with metformin alone and 38.6% of patients treated with rosiglitazone plus metformin.[18] Although our failure rates were lower than those seen in the TODAY study, we cannot infer whether the improved results are due to the more intensive treatment regimen we used or due to a more severe disease state in the young patients with type 2 diabetes enrolled in the TODAY study.

We found several patient characteristics that predicted treatment failure. Interestingly, at the initial visit, when patients were universally hyperglycemic and metabolically decompensated, there were no failure predictors. However, after 3 months of intensive insulin and metformin therapy, when average Hb_{A1c} declined from above 10% to below 6%, there were several predictive variables. The patients who eventually failed had higher systolic blood pressure, fasting glucose (although within near-normal range), fasting C-peptide, and lower insulin sensitivity. Therefore, these patients, while still well compensated at this time point, had features of more advanced insulin resistance, which explains the propensity to treatment failure. Patients who failed after randomization to TOT treatment had significantly lower insulin sensitivity compared with those who did not fail (Fig. 4F), suggesting that perhaps those who did not respond to the insulin-sensitizing effect of pioglitazone were those who failed the treatment. This is in contrast to both the TODAY and ADOPT analyses that found lower baseline β-cell function and higher Hb_{A1c} in the patients who failed.[19,20] The difference in our findings could be explained by the fact that in both ADOPT and TODAY studies, baseline β-cell function was evaluated before treatment initiation, whereas in our study, we measured the baseline β-cell function after a 3-month initial treatment with insulin and metformin during which maximal β-cell

recovery occurred. Our patients had much worse metabolic derangements at baseline but any glucolipotoxicity was reversed before the randomization, when the first β-cell function analysis occurred, and perhaps that is why we did not observe lower initial β-cell function in those who would eventually fail. Furthermore, we believe that the Matsuda index provides a better estimate of insulin sensitivity than the homeostatic model assessment of insulin resistance used in either of these studies, and perhaps a reason why we were able to note insulin resistance as a predictor of treatment failure. At the visit (3–6 months) before failure, the group who failed had worse fasting glucose, Hb_{A1c}, and β-cell function, these being warning signs that a failure is impending. The slope of β-cell function decline in the treatment failure group was much higher compared with the group that did not fail treatment (who had preserved β-cell throughout the study follow-up; Figs. 4G, H), suggesting that β-cell decompensation is the event closely preceding the failure event. In summary, our findings suggest that treatment failure occurs in patients who have worse insulin resistance at baseline, which is the first noticeable abnormality occurring months to years before failure. β-Cell decompensation, on the other hand, occurs in closer proximity to the time of failure and is the final pathophysiologic event leading to the failure.

After failure, despite switch to insulin therapy (in the TOT group) or intensification of therapy (in the INS group), at the final study visit, patients continued to have worse Hb_{A1c}, β-cell function, and insulin sensitivity despite significantly higher doses of insulin. Thus, once patients experience worsening of glycemic control, they are unlikely to regain glycemic control and improve β-cell function. This finding further supports the need to use all available tools to prevent treatment failure in the first place, as once failure ensures subsequent rescue of glycemic control is unlikely.

Importantly, neither treatment regimen was superior at preserving β-cell function, preventing decline in insulin sensitivity or preventing treatment failure. Since the initiation of this study in 2003, the paradigm for diabetes management has shifted with the rise in popularity of glucagonlike peptide 1–based therapy and the fall from favor of thiazolidinediones (TZDs).[21] The TZD component of our TOT regimen likely contributed to its success in maintaining glycemic control through its pleotropic effects on β-cell function, peripheral insulin sensitivity, and possible preservation of β-cell mass.[22] Although the insulin sensitivity fell in the TOT group over time, this seems to be primarily occurring in participants who failed therapy (treatment nonresponders; Fig. 4F). Glucagonlike peptide 1 drugs have been shown to primarily improve β-cell function (with indirect effects on insulin sensitivity) and are more effective in this regard than TZDs.[23,24] Incorporating these newer drugs early in treatment could potentially have equal or greater effects in stabilizing the disease process.[25]

It is also important to note the high acceptance rate of insulin therapy and that all quality-of-life parameters were similar regardless of the treatment regimen. These findings confirm that insulin treatment is well accepted by patients even in the very early stages of the disease and does not alter quality of life; therefore, it can be safely considered as a viable treatment option at any stage of the disease.

Overall, this study shows that β-cell function and glycemic control can be maintained at a stable level for at least 6 years after diagnosis if an intensive treatment algorithm is initiated at the time of diagnosis of type 2 diabetes. Treatment failures occurred in patients with lower insulin sensitivity at baseline and those who experienced greater β-cell decline over the course of the study. Identification of patients at high risk of treatment failure is important because rescue therapy is unlikely to be successful once treatment failure ensues.

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REFERENCES

1. El-Assaad W, Buteau J, Peyot ML, et al. Saturated fatty acids synergize with elevated glucose to cause pancreatic beta-cell death. *Endocrinology*. 2003;144(9):4154–4163.
2. Steffes MW, Sibley S, Jackson M, et al. Beta-cell function and the development of diabetes-related complications in the diabetes control and complications trial. *Diabetes Care*. 2003;26(3):832–836.
3. ORIGIN Trial Investigators, Gerstein HC, Bosch J, et al. Basal insulin and cardiovascular and other outcomes in dysglycemia. *N Engl J Med*. 2012;367(4):319–328.
4. Ilkova H, Glaser B, Tunçkale A, et al. Induction of long-term glycemic control in newly diagnosed type 2 diabetic patients by transient intensive insulin treatment. *Diabetes Care*. 1997;20(9):1353–1356.
5. 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.
6. Ryan EA, Imes S, Wallace C. Short-term intensive insulin therapy in newly diagnosed type 2 diabetes. *Diabetes Care*. 2004;27(5):1028–1032.
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, et al. 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. Kahn SE, Haffner SM, Heise MA, et al. Glycemic durability of rosiglitazone, metformin, or glyburide monotherapy. *N Engl J Med*. 2006;355(23):2427–2443.
10. Turner RC, Cull CA, Frighi V, et al. Glycemic control with diet, sulfonylurea, metformin, or insulin in patients with type 2 diabetes mellitus: progressive requirement for multiple therapies (UKPDS 49). UK Prospective Diabetes Study (UKPDS) Group. *JAMA*. 1999;281(21):2005–2012.
11. Harrison LB, Adams-Huet B, Raskin P, et al. β-cell function preservation after 3.5 years of intensive diabetes therapy. *Diabetes Care*. 2012;35(7):1406–1412.
12. Lingvay I, Kaloyanova PF, Adams-Huet B, et al. Insulin as initial therapy in type 2 diabetes: effective, safe, and well accepted. *J Investig Med*. 2007;55(2):62–68.
13. Lingvay I, Legendre JL, Kaloyanova PF, et al. Insulin-based versus triple oral therapy for newly diagnosed type 2 diabetes: which is better? *Diabetes Care*. 2009;32(10):1789–1795.
14. Matsuda M, DeFronzo RA. Insulin sensitivity indices obtained from oral glucose tolerance testing: comparison with the euglycemic insulin clamp. *Diabetes Care*. 1999;22(9):1462–1470.
15. Radaelli T, Farrell KA, Huston-Presley L, et al. Estimates of insulin sensitivity using glucose and C-Peptide from the hyperglycemia and adverse pregnancy outcome glucose tolerance test. *Diabetes Care*. 2010;33(3):490–494.

16. Kahn SE, Prigeon RL, McCulloch DK, et al. Quantification of the relationship between insulin sensitivity and beta-cell function in human subjects. Evidence for a hyperbolic function. *Diabetes*. 1993;42(11):1663–1672.
17. Copeland KC, Zeitler P, Geffner M, et al. Characteristics of adolescents and youth with recent-onset type 2 diabetes: the TODAY cohort at baseline. *J Clin Endocrinol Metab*. 2011;96(1):159–167.
18. TODAY Study Group, Zeitler P, Hirst K, et al. A clinical trial to maintain glycemic control in youth with type 2 diabetes. *N Engl J Med*. 2012;366(24):2247–2256.
19. TODAY Study Group. Effects of metformin, metformin plus rosiglitazone, and metformin plus lifestyle on insulin sensitivity and β-cell function in TODAY. *Diabetes Care*. 2013;36(6):1749–1757.
20. Kahn SE, Lachin JM, Zinman B, et al. Effects of rosiglitazone, glyburide, and metformin on β-cell function and insulin sensitivity in ADOPT. *Diabetes*. 2011;60(5):1552–1560.
21. Inzucchi SE, Bergenstal RM, Buse JB, et al. Management of hyperglycemia in type 2 diabetes: a patient-centered approach: position statement of the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). *Diabetes Care*. 2012;35(6):1364–1379. Erratum in: Diabetes Care. 2013;36(2):490.
22. Yki-Järvinen H. Thiazolidinediones. *N Engl J Med*. 2004;351(11):1106–1118.
23. DeFronzo RA, Triplitt C, Qu Y, et al. Effects of exenatide plus rosiglitazone on beta-cell function and insulin sensitivity in subjects with type 2 diabetes on metformin. *Diabetes Care*. 2010;33(5):951–957.
24. Preumont V, Hermans MP, Brichard S, et al. Six-month exenatide improves HOMA hyperbolic product in type 2 diabetic patients mostly by enhancing beta-cell function rather than insulin sensitivity. *Diabetes Metab*. 2010;36(4):293–298.
25. Abdul-Ghani M, Puckett C, Adams J, et al. Initial triple combination therapy is superior to stepwise add-on conventional therapy in newly diagnosed T2DM. *Diabetes*. 2013;62(Supplement 1):A1–A98.