Influence of Intensive Diabetes Treatment on Quality-of-Life Outcomes in the Diabetes Control and Complications Trial

THE DIABETES CONTROL AND COMPLICATIONS TRIAL RESEARCH GROUP

OBJECTIVE — To evaluate the effect of intensive diabetes treatment on patient quality of life assessed by the Diabetes Quality-of-Life Measure, the Symptom Checklist-90R, the Medical Outcome Study 36-Item Short Form Survey, and intercurrent psychosocial events in the Diabetes Control and Complications Trial (DCCT).

RESEARCH DESIGN AND METHODS — The DCCT was a 29-center prospective controlled clinical trial that demonstrated the beneficial effect of intensive diabetes treatment on retinopathy, nephropathy, and neuropathy. The 1,441 volunteers with IDDM, aged 13–39 years, were randomly assigned to intensive or conventional diabetes therapy. The volunteers were followed for a mean of 6.5 years (range 3–9 years). Quality-of-life data were collected during annual visits. Of the volunteers, 99% completed the study, and >95% of scheduled tests were completed.

RESULTS — All analyses of quality of life, psychiatric symptom indexes, and psychosocial event data showed no differences between intensive and conventional diabetes treatment.

CONCLUSION — Under careful treatment conditions, such as those followed in the DCCT, patients undergoing intensive diabetes treatment do not face deterioration in the quality of their lives, even while the rigor of their diabetes care is increased.

Outcomes of clinical trials typically have been evaluated by measures of time to a clinical event or relapse and percentage survival, along with physiological and anatomical markers of disease progression. However, other measures of treatment outcome, such as the quality of a patient's life, may be useful in assessing the effects of an intervention (1–5). Quality of life is usually measured from the patient's perspective. Assessment of quality of life in a clinical trial must focus on a person's illness and treatment experience. This can include judgments about satisfaction with treatment, social and role functions, emotional well-being, and physical symptoms. Several reasons have been put forth for broadening clinical trial outcomes to include such health-related quality-of-life assessments. For example, treatments may yield similar medical outcomes but have different symptom experiences (1,2), and treatments may involve a considerable degree of suffering (3). In many instances, patient and health care provider decisions about treatment depend on the degree to which patients feel better or worse while undergoing a particular treatment. Thus, the effects of treatment on quality of life may be valuable in translating the results of a trial into practical clinical decision-making (4). This is of special relevance to chronic illnesses, such as IDDM, in which years may pass before the effectiveness of a therapy becomes clinically evident. Therefore, personal treatment decisions usually include an evaluation of the burdens of treatment and its side effects.

The Diabetes Control and Complications Trial (DCCT) faced some of these issues, including substantially different personal time demands between intensive and conventional treatments and the possibility that medical outcomes would only be demonstrable in terms of subtle physiological and anatomical markers of disease progression (6,7). To compare fully the benefits and personal costs of the two treatment regimens, quality-of-life assessments were included along with more traditional measures of disease progression.

The DCCT, a multicenter prospective controlled clinical trial, was designed to compare the effects of intensive diabetes therapy with those of conventional diabetes therapy on the development and/or progression of long-term complications of IDDM. The goal of intensive therapy was to achieve glycemic control as close to the nondiabetic range as possible while minimizing hypoglycemia (6–8). In addition to studying the development and progression of retinopathy, the principal study endpoint, other outcome assessments included evaluations of renal, neurological, cardiovascular, neuropsychological, and quality-of-life status. Results of the DCCT demonstrated that intensive treatment led to striking risk reductions in the onset and progression of retinopathy, nephropathy, and neuropathy (8). Initial analyses did not demonstrate differences in the quality-of-life outcomes between the treatment groups (8).

This study examines, in greater depth, the effect of intensive versus conventional diabetes treatment on quality of life as assessed by the Diabetes Quality-of-Life Measure (DQOL), the Symptom Checklist-90R (SCL-90R), the Medical Outcome Study 36-Item Short Form Survey (SF-36), and intercurrent psychosocial events. Multiple indexes of quality of life were used as outcomes because no single standard measure exists for assessing the effects of clinical interventions on diabetes. In addition, this study examines the influence of baseline characteristics,

From The Diabetes Control and Complications Trial (DCCT) Research Group, Bethesda, Maryland.

A complete listing of the DCCT Research Group is available in *Diabetes Care* 18:361–376, 1995.

Address correspondence and reprint requests to DCCT Research Group, Box NDIC/DCCT, Bethesda, MD 20892.

Received for publication 26 January 1995 and accepted in revised form 28 September 1995.

DCCT, Diabetes Control and Complications Trial; DQOL, Diabetes Quality-of-Life Measure; GSI, Global Severity Index; RR, relative risk; SCL-90R, Symptom Checklist-90R; SES, socioeconomic status; SF-36, Medical Outcome Study 36-Item Short Form Survey.

such as the presence or absence of early complications, IDDM duration, sex, and social class, on quality-of-life outcomes. Finally, this study explores the effect of frequency of severe hypoglycemia on quality of life.

RESEARCH DESIGN AND METHODS

— The overall design, selection criteria, and description of measures used in the DCCT have been described in full (6). For purposes of this report, however, the following points should be noted.

1. At study entry, the patients were between 13 and 39 years of age and had a short duration of IDDM (1–5 years for the primary prevention trial and 1–15 years for the secondary intervention trial) (6). Table 1 presents the baseline characteristics of the 1,441 patients.
2. Upon study entry, the complications of diabetes were either absent (primary prevention cohort) or mild (secondary intervention cohort).
3. The recruitment and selection process was designed to include volunteers who were knowledgeable about the trial and who were willing to be assigned randomly to a treatment. In addition, volunteers were selected for their anticipated ability to adhere to either the intensive or conventional treatment regimen and to participate in a trial lasting as long as 10 years (9,10).
4. Patients in the intensive treatment group were given the goal of achieving near-normal glycemic levels, a task with extensive demands. Intensive therapy included insulin injections at least three times per day or insulin administration via constant subcutaneous infusion, blood glucose monitoring at least four times per day with algorithms for dosage adjustment, 3:00 A.M. blood glucose testing once a week, vigorous attention to the effects of diet and exercise on blood glucose, at least monthly clinic visits for medical supervision and psychological support, and frequent telephone contacts for treatment review and adjustment (7,8).
5. Patients in the conventional treatment group were treated with one or two insulin injections per day, daily blood or urine glucose monitoring, dietary instruction, and follow-up visits at 3-month intervals (7,8).
6. The entire cohort of 1,441 patients was followed for a mean of 6.5 years (range 3–9 years), a total of >9,300 patient-years. Of the patients, 99% completed the study, and >95% of all scheduled examinations were completed. Eleven patients died, and 32 patients, 8 of whom were lost to follow-up, were assigned to inactive status for some time during the trial because of their unavailability for study or because of the investigator's decision that continuation of treatment would be hazardous.

Table 1—*Demographic and clinical variables at baseline*

Variable	Treatment group	
	Intensive	Conventional
n	711	730
Demographics		
Sex (% women)	49	46
Age at entry (years)	27 ± 0.3	27 ± 0.3
Race (% white)	97	96
Mean education (years)		
Adult	15 ± 2	15 ± 2
Adolescent	11 ± 1	10 ± 1
Hollingshead social class (%)		
Class I	29	31
Class II	22	23
Class III	20	15
Class IV	20	23
Class V	3	3
Missing	6	5
Marital status (%)		
Never married	45	45
Married or remarried	48	50
Separated	1	1
Divorced	5	4
Widowed	0.1	0.1
Clinical		
Duration of diabetes (months)	70 ± 2	66 ± 2
HbA_{1c}	9 ± 0.1	9 ± 0.1
Mean blood glucose (mg/dl)	234 ± 3	231 ± 3
Any retinopathy (%)	51	48
Overweight (%)	6.9	8.4
Hypoglycemia in year before DCCT		
Required medical assistance (%)	5	4
Loss of consciousness (%)	5	5
Psychosocial history		
Heavy drinkers (>560 g/week) (%)	0.1	0.0
Suicide attempts (%)	0.4	0.5
Psychiatric hospitalization (%)	0.7	1.1
SCL-90R GSI ≥63 (%)	9.4	10.1

Data are means ± SE. All adolescent subjects were unmarried at baseline.

Quality-of-life measures

The DQOL. The DQOL is a self-administered multiple-choice 46-item assessment designed specifically for the DCCT. Because it was possible that the demands of intensive versus conventional treatments would lead to different levels of patient burden, the DQOL was administered to assess patients' perceptions of impact and satisfaction with specific features of diabetes management (11). This disease-specific measure was developed

for use in the trial because of the possibility of greater sensitivity to treatment effects than available generic measures. This measure has several useful features: it can be used in both adolescents and adults, and because items do not identify specific types of treatment (e.g., insulin, pump, or self-monitoring), it is applicable to patients who are using different methods of diabetes management.

The DQOL has four primary scales (satisfaction, impact, diabetes worry, and social/vocational worry) that assess different aspects of quality of life. Satisfaction is rated from 1 (very satisfied) to 5 (never satisfied). Impact and worry scales are rated from 1 (no impact and never worried) to 5 (always affected and always worried). The DQOL and a method of scoring the DQOL have been described previously (12,13). The current scoring system yields scale scores that range from 0 (lowest quality of life) to 100 (highest quality of life). To obtain this type of scale, the original score is subtracted from 5 and then multiplied by 25. This scaling is obtained using a method identical to the procedure for scoring the SF-36 quality-of-life measure (14). In addition to the primary scales and a total score, a global health perception rating is derived from a single item that asks patients to compare their health with that of other individuals their age (15).

Psychometric studies (11,12) have indicated that the overall DQOL measure has excellent internal consistency (Cronbach's $\alpha = 0.92$) for both adults and adolescents. In a study of patients with demographic and clinical characteristics similar to those of the DCCT sample, internal consistency for all subscales was >0.70 (11). Test-retest reliability over an average period of 9 days was 0.92 for the overall measure (11). The DQOL has demonstrated convergent validity with conceptually relevant measures of well-being, psychiatric symptoms, and adjustment to illness (11). Also, other studies have shown that the DQOL discriminates between patients with different numbers of clinically evident complications (12) and is sensitive to different therapies for NIDDM (12) and to a change in therapy for IDDM (i.e., pancreatic transplantation) (16).

The DQOL was administered annually throughout the study. However, the 278 patients who began treatment during the trial's feasibility phase completed the forms at 6-month intervals during the first 2 years of follow-up to evaluate whether intensive treatment led to early changes in quality of life. When initial analyses did not reveal group differences, the frequency of testing was reduced to yearly intervals for all patients (7).

A decrease of 12.5 points on the total DQOL score was used as the definition of an adverse quality-of-life event for endpoint analyses. This definition was derived from recent studies comparing patients, through use of the DQOL, who had different numbers of complications and types of treatment (12,13,16). In one study (12), there was a mean total DQOL score difference of 25 scale points between patients with three clinically evident microvascular complications and those with no complications. In another study (16), patients given a combined kidney-pancreas transplant had a 25-point improvement on the DQOL. These represented large effects, beyond those anticipated in the DCCT. Therefore, we chose a smaller effect that represented the effect of one or two complications or a smaller change in therapy as our data-analytic definition of change in DQOL-rated quality of life. In addition, DQOL data were analyzed using the total score as a continuous rating of quality of life.

The SCL-90R. The SCL-90R is a 90-item test that is used widely to measure psychiatric symptoms (17,18). Because it was anticipated that the burden of the trial might lead to psychological distress, the SCL-90R was incorporated into the trial as one way to characterize quality of life. This instrument has been subjected to multiple assessments of reliability and validity in a range of populations, including individuals with chronic physical illness (17,18). The SCL-90R has excellent internal consistency for subscales (Cronbach's $\alpha = 0.77$–0.90) and test-retest reliability (0.78–0.90) over a 1-week period (17,18). Validity data for the SCL-90R include correlation in expected directions with other measures reflecting psychiatric symptoms (17,18).

The SCL-90R consists of self-rated symptoms occurring during the previous week. The scoring system allows the determination of overall psychiatric distress as well as specific components. Answers are scored in terms of overall measures of psychiatric distress (Global Severity Index [GSI], Positive Symptoms Distress Index, and Positive Symptom Total) or with respect to nine dimensions of symptoms that assess more specific aspects of distress (somatization, obsessive-compulsive, interpersonal sensitivity, depression, anxiety, hostility, phobic anxiety, paranoid ideation, and psychoticism). The raw scores are converted to *T*-scores (mean = 50; SD = 10) for purposes of analysis. The *T*-scores were calculated using normative data from a sample of nondiabetic patients (493 men and 480 women) (18). Thus, a DCCT patient who has a *T*-score of 50 is scoring at the average of subjects from this large sample.

The SCL-90R was administered annually throughout the study. A psychiatric event was defined as any occurrence of a SCL-90R GSI score ≥63. We chose this definition for outcome analyses because previous studies have suggested that a normalized *T*-score of ≥63 may be used to identify patients who are likely to have a current psychiatric disorder (18). For these analyses, patients who had a GSI score ≥63 at baseline were eliminated. It should be noted that many patients screening positive for psychiatric disorders using this criteria would be found to have short-lived psychiatric conditions such as adjustment disorders. Other analyses of DCCT participants used the SCL-90 data as a continuous rating of emotional distress.

The SF-36. The SF-36 is a third relevant measure of quality of life. The SF-36 was not available at study inception. It was given to all DCCT patients at study end to provide comparison information with data from other studies, to evaluate areas of functioning not well covered by the DQOL (e.g., physical functioning), and to help perform economic analyses of the cost-benefit ratio of the proposed follow-up to the trial (19). Recent research has suggested that a single utility index can be derived from the SF-36 (20). The SF-36 is generic (not disease-specific) and uses 36 items to assess several facets of functional health status, including physical and emotional role functioning, pain, mental health, fatigue, and perception of general health. It has been subjected to numerous evaluations of reliability and validity (12,14,21,22). The scores, which represent the percentage of the total possible scores achieved, range from 0 to 100; a higher score indicates a more favorable health state.

Intercurrent psychosocial events. Intercurrent psychosocial events were gathered

from quarterly, annual, and end-of-study historical interviews. These interviews included information about education level, marital status, psychiatric treatment, psychiatric hospitalization, and suicide attempts.

Hypoglycemic events. Hypoglycemic events were recorded from patient reports at regular follow-up visits and provider-patient telephone contacts between visits. The analytic definitions of severe hypoglycemia were the same as used in prior DCCT reports (10,23). We analyzed the influence of severe hypoglycemia on quality of life using the definition that included all severe hypoglycemic events requiring assistance and the definition that included the subset of severe hypoglycemic episodes resulting in coma or seizure.

Data analysis

The Wilcoxon's rank-sum test was used to compare the two groups for ordinal and numerical variables (24). The contingency χ^2 was used for categorical variables (24). Psychiatric event rates were expressed as number of events per 100 patient-years based on the ratio of observed number of events (cases) to the total patient-years of follow-up. The life-table method was used to express the cumulative incidence of an event based on the time to first event. The average relative risk (RR) (intensive:conventional), comparing the two treatment groups over the complete period of observation, was estimated by a proportional-hazards analysis that was stratified by absence or presence of complications at baseline and the baseline level of the corresponding outcome measure (25). The difference between cumulative incidence curves was tested using the Wald test for estimated RR (25).

The comparison of the treatment groups with respect to the prevalence of these events over time was assessed using the multivariate analysis of log RR (26). The comparison of groups with respect to multiple quantitative measurements was assessed using the multivariate Mann-Whitney nonparametric analysis (27). The overall test of group differences in these multivariate analyses was performed using the nonparametric test of stochastic ordering proposed by Lachin and Wei (26) with equal weights applied to the corresponding univariate Mann-Whitney difference summary statistics.

Table 2—*Diabetic quality of life and SCL-90R scores at baseline and study end*

	Baseline		Study end	
	Intensive	Conventional	Intensive	Conventional
Quality of Life				
Total score	78 ± 8	78 ± 9	78 ± 9	78 ± 9
Impact	76 ± 8	76 ± 8	75 ± 8	75 ± 9
Satisfaction	73 ± 12	73 ± 13	74 ± 13	74 ± 14
Diabetes-related worry	80 ± 12	80 ± 13	81 ± 13	80 ± 13
Social-vocational worry	81 ± 14	81 ± 14	78 ± 16	79 ± 17
Global health perception	79 ± 15	79 ± 15	80 ± 16	77 ± 16
SCL-90R				
Global severity index	50 ± 10	50 ± 10	48 ± 10	50 ± 12
Anxiety	49 ± 10	50 ± 10	47 ± 9	49 ± 11
Depression	50 ± 10	50 ± 10	50 ± 12	51 ± 13
Hostility	50 ± 10	50 ± 10	49 ± 9	49 ± 9
Interpersonal sensitivity	51 ± 11	52 ± 11	50 ± 10	50 ± 11
Obsessive compulsion	50 ± 10	50 ± 10	50 ± 10	51 ± 11
Paranoid ideation	48 ± 9	48 ± 9	47 ± 9	48 ± 9
Phobic anxiety	47 ± 8	48 ± 7	47 ± 7	48 ± 7
Psychoticism	50 ± 1	50 ± 11	48 ± 10	50 ± 11
Somatization	49 ± 9	49 ± 9	48 ± 8	49 ± 9

Data are means ± SD. At study end, n = 684 for the intensive group and n = 705 for the conventional group. Quality-of-life scores range from 0 to 100, with 100 indicating a more favorable quality of life. SCL-90R scores are normalized T-scores (mean = 50; SD = 10).

The comparison of the treatment groups using the SF-36 scores was performed with the Wilcoxon's rank-sum test (24). Using the time-dependent variable of occurrence of severe hypoglycemia, we also examined the effect of hypoglycemia on subsequent SCL-90R and DQOL events. This analysis was conducted using a proportional-hazards regression model with history of hypoglycemia as a time-dependent covariate (28). Analyses of the intensive and conventional treatment groups were conducted separately. Exclusion criteria pertaining to the number of hypoglycemic episodes in the year before entry differed between the phase II (feasibility) subjects and the phase III subjects. Therefore, the regression model was stratified by phase and by primary prevention and secondary intervention cohort status. All results nominally significant at ($P < 0.05$) are indicated.

RESULTS

DQOL and SCL-90R changes over time

There were no significant differences at baseline between the conventionally and intensively treated patients on either the DQOL or SCL-90R scales (Table 2). End-of-study assessments showed that the scores on all scales did not differ between the treatment groups (Table 2). Figure 1*A* and *B* depicts the cumulative percentage of patients in each treatment group having quality-of-life events as indexed by a >12.5-point decrease on the DQOL and a GSI T-score of ≥63, respectively. There were no differences between the intensively treated patients and the conventionally treated patients in the cumulative incidence of these events. Because cumulative incidence ignores subsequent progression or regression after an event, we also examined the prevalence of events at each annual assessment. Examinations of the point prevalence of DQOL and SCL-90 events also revealed that the percentage of events did not differ between groups (data not shown). Excluding patients with the SCL-90 event at baseline, 24.8% of intensively treated patients and 25.0% of conventionally treated patients had at least one quality-of-life psychiatric event (defined by SCL-90R) during the full length of the study. The DQOL event could not have occurred at baseline because it is defined as a change from baseline; 14.6% of intensively treated patients and 13.2% of conventionally treated patients had at least one such event during the study.

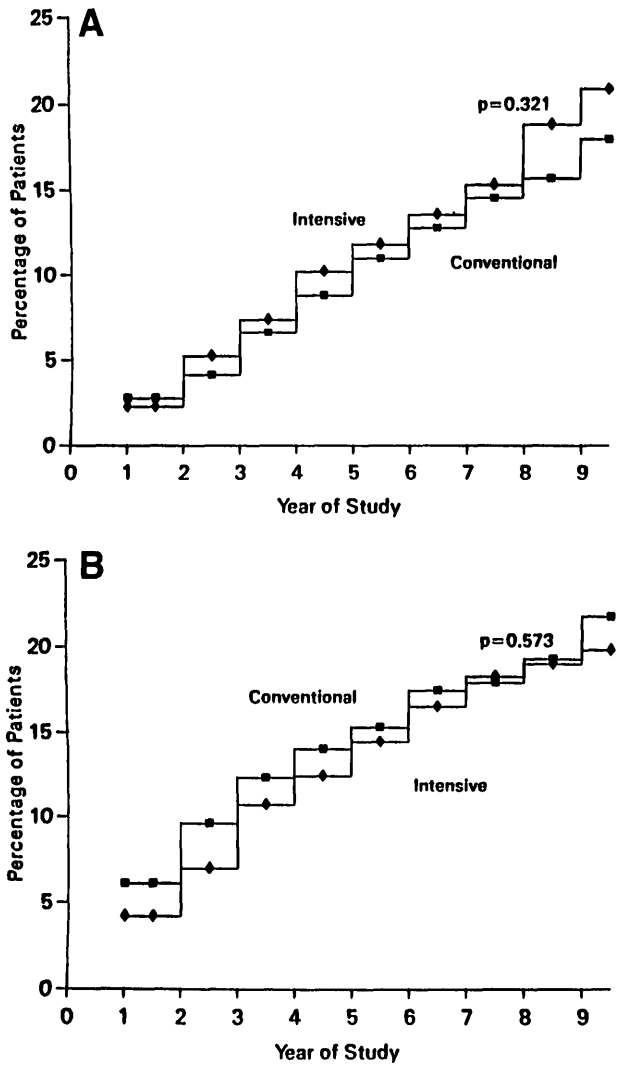

Figure 1—A: *cumulative incidence of DQOL core decrease of ≥12.5 in patients with IDDM receiving intensive therapy (◆) or conventional therapy (■). The average adjusted RR (intensive:conventional) of developing this event using the proportional-hazards model was 1.19 (P = 0.321).* B: *cumulative incidence of SCL-90-R GSI T-score ≥63 in patients with IDDM receiving intensive therapy (◆) or conventional therapy (■). The average adjusted RR (intensive:conventional) of developing this event using the proportional-hazard model was 0.90 (P = 0.573). Patients with the event at baseline have been eliminated from the analysis.*

Functional health status at study end

No differences were found between intensively treated patients and conventionally treated patients on the SF-36 scales at study end. The mean percentile scores (intensive versus conventional) for the various scales were as follows: physical functioning (94 vs. 94); social functioning (93 vs. 92); role functioning, physical (90 vs. 89); role functioning, emotional (87 vs. 85); mental health (76 vs. 76); energy/fatigue (59 vs. 60); pain (84 vs. 83); and general health perception (72 vs. 69).

Adverse events

Table 3 summarizes the psychosocial events evaluated in patients followed in the DCCT. Examination of these intercurrent events failed to demonstrate any difference in rates of divorce, occurrence of psychiatric illnesses that required hospitalization, or number of suicide attempts. Examination of important developmental achievements for adolescents showed that the two treatment groups reached identical levels of education and rates of marriage.

Baseline subgroups

To determine whether treatment effects obtained in the entire study cohort applied to different subgroups of patients, we examined the influence of baseline characteristics on the rates of DQOL and SCL-90R outcomes. Characteristics such as primary prevention versus secondary intervention status, sex, age, and duration of diabetes showed similar treatment effects for both the DQOL and SCL-90R outcomes, with no differences in quality-of-life outcome between treatment groups. A significant treatment group-by-social class interaction was found on the SCL-90 outcome ($P = 0.01$). Intensively treated patients in the lowest social classes (socioeconomic status [SES] classes IV and V) appeared to experience fewer psychiatric events than patients from those classes in the conventional treatment group. (The rates per 100 patient-years of SCL-90 events were 2.7, 3.1, 3.4, 2.7, and 2.2 for SES classes I through V, respectively, in the intensive group and 2.0, 2.7, 3.6, 5.2, and 4.3 for SES classes I through V, respectively, in the conventional group.) Examination of the DQOL did not reveal any significant interactions between treatment and social class.

Relationship of hypoglycemia to quality-of-life outcomes

We modeled the relationship of hypoglycemia (during the study but before the occurrence of quality-of-life outcomes) to the SCL-90R and DQOL outcomes. Models were fit separately for each treatment group. One model used the definition of hypoglycemia that incorporated all severe hypoglycemic events requiring assistance. Another model used severe hypoglycemia that resulted in coma or seizure. Two variables were used to describe the prior history of hypoglycemia: any prior hypoglycemia (yes or no) and the number of prior episodes. The values of these variables changed over time as successive episodes of hypoglycemia occurred. In addition to the time-dependent hypoglycemia variables, each full model included variables for age (adults versus adolescents), age at diagnosis of diabetes, total months of IDDM duration at entry, sex (men versus women), marital status (married versus unmarried), BMI at baseline, albumin excretion rate at baseline, level of retinopathy at baseline, history of hypoglycemia before entry into the DCCT, *T*-score for GSI at baseline, total DQOL score at baseline, and SCL-90R outcome. In Table 4, we present models examining the association between hypoglycemia resulting in coma or seizure and GSI. This was the only model in which frequency of prior

Table 3—*Psychosocial events during the DCCT*

	Treatment group	
	Intensive	Conventional
Marriages	4.18	4.18
Total number of events	195	197
Adolescent	19	22
Adult	176	175
Divorces	1.93	1.78
Total number of events	90	84
Years of education at study end		
Adolescents	14.27 ± 2.0	14.20 ± 2.0
Adults	15.26 ± 2.4	15.26 ± 2.4
Psychiatric illness with hospitalization	0.49	1.11*
Total number of events	23	53
Number of patients with event	13	22
Psychiatric illness requiring treatment	1.46	1.91
Number of patients with event	47	47
Total number of events	69	91
Classification of event		
Depressive episode	38	42
Bipolar disorder	6	5
Eating disorder	2	9
Substance abuse	6	8
Attempted suicide	2	6
Emotional problem/anxiety	8	7
Other	7	14
Forms of interventions used (*n*)		
Medication	47	51
Counseling	64	88
Other form of treatment	8	12
Number of patients reporting a suicide attempt at study end	3	8†

Data for marriages, divorces, and psychiatric illnesses are rate per 100 patient-years: 4,668 patient-years of follow-up in intensive treatment group; 4,716 patient-years of follow-up in conventional treatment group. Data for years of education at study end are means ± SE. *P = 0.068, †P = 0.23 for intensive vs. conventional treatment.

hypoglycemic events was associated with quality of life. This was found only in the intensive treatment group (P = 0.008 on 2 df), and the effect persisted after adjustment for the other covariates (P = 0.02 on 2 df). In both treatment groups, the GSI T-score at baseline is the dominant, albeit weak, factor associated with the occurrence of a subsequent change in quality of life (R^2 = 4%). In the conventional treatment group, the total DQOL score at baseline was significant ($P < 0.0001$, R^2 = 2%). Demographic variables that were significant were sex in the intensive treatment group (R^2 = 1%) and age status in the conventional group (R^2 = 2%). Prior hypoglycemia played some additional role within the intensive treatment group (R^2 = 1%, P = 0.02 on 2 df). The adverse effect on quality of life was most evident for patients who had three or more hypoglycemic episodes that resulted in coma or seizure. These individuals had an RR for an adverse effect on quality of life that was 40% higher than that for patients without hypoglycemia. Further analysis revealed that this effect was significant in the intensive treatment group of the primary prevention cohort but not in the secondary intervention cohort. The effect was the same after adjustment for other factors in the model. Furthermore, a significant effect of hypoglycemia was noted for three SCL-90R subscale outcomes in addition to the GSI: depression, interpersonal sensitivity, and paranoid ideation. As before, these effects were evident only in the intensive treatment group of the primary prevention cohort.

The models using DQOL score as the outcome did not demonstrate an association of hypoglycemia with an adverse change in quality of life.

CONCLUSIONS— All quality-of-life, symptom index, and psychosocial event data gathered during the DCCT provided clear evidence that both intensive and conventional treatment afforded patients similar levels of well-being. The fact that average symptom scores did not change, point prevalence of psychiatric events did not increase, and adverse events such as psychiatric hospitalization occurred at low rates suggests that the DCCT volunteers remained psychologically healthy as a group throughout the trial. Moreover, these data show that the occurrence of severe hypoglycemia was not consistently associated with a subsequent increase in symptomatic distress or decline in diabetes-related quality of life. However, in the primary prevention intensive treatment group, patients who had repeated severe hypoglycemia (three or more events resulting in coma or seizure) tended to be at increased risk of measurable symptomatic distress. Because we performed multiple assessments of the effects of hypoglycemia on quality-of-life outcomes, one must be cautious about interpreting this single positive finding.

Taken together, these findings indicate that under careful treatment conditions, such as those followed in the DCCT, patients treated intensively, with the goal of achieving glycemic control as close to normal levels as possible, do not face deterioration in the quality of their personal lives despite the increasing demands of their diabetes care and the increased frequency of hypoglycemia. These results are consistent with earlier pilot data from evaluations of intensive diabetes management strategies in small groups of select research volunteers followed over short time periods (29–31). In those studies, intensive diabetes treatment was associated with either no change in psychosocial and social functioning or modest improvement in psychological function, such as perception of well-being or level of anxiety.

Several factors may account for the findings from the DCCT.

1. It is reasonable to assume that the increased demands and potential stress of an intensive diabetes program may be countered by the im-

Table 4—*Proportional hazards regression models for SCL-90R GSI*

Covariates	Treatment group: Intensive RR	Intensive (95% CI)	Conventional RR	Conventional (95% CI)
Prior hypoglycemia history				
Any hypoglycemia resulting in coma/seizure during study (yes versus no)	0.79	(0.43–1.46)	1.79	(0.66–4.85)
Number of prior episodes during the study	1.21	(1.05–1.40)	0.81	(0.50–1.32)
Other covariates				
GSI at baseline	1.11	(1.07–1.14)	1.11	(1.07–1.15)
DQOL at baseline	1.94	(0.88–4.24)	4.31	(2.13–8.70)
Women versus men	0.54	(0.36–0.82)	0.93	(0.62–1.39)
Adult versus adolescent	0.54	(0.23–1.28)	0.20	(0.09–0.42)

RR indicates a per unit change of the covariate or for one category versus another. Effects are multiplicative, e.g., in the intensive group, after one prior episode of hypoglycemia, the risk is (0.79) (1.21) = 0.96 times that of subjects with no prior episodes; after two episodes, the risk of a GSI ≥ 63 is $(0.79)(1.21)^2 = 1.16$ times that of subjects with no prior episodes. Test for the effect of prior hypoglycemia history on 2 df. $P < 0.02$ in the intensive group, not significant in the conventional group. Other covariates were nominally significant at ($P < 0.05$) in either group if shown. Other baseline covariates not nominally significant in both treatment groups were age at diagnosis of IDDM, duration of IDDM, married versus unmarried, BMI, albumin excretion rate, retinopathy grade, and a history of hypoglycemia.

proved sense of well-being derived from improved glycemic control, less fluctuation in blood glucose concentration, and greater comfort in the sense of control over one's illness (30). These patient-perceived benefits may counterweigh both the demands of the treatment and the adverse impacts, such as the increased rate of severe hypoglycemia.

2. The study was constructed to provide patients who were assigned to intensive treatment close and continuous follow-up by treatment teams dedicated to study goals and their patients' care. These teams consisted of diabetologists, nurses, nutrition specialists, and mental health professionals experienced in the care of diabetes and the complexities of intensive diabetes management. The teams had ample time to care for DCCT subjects; indeed, patients were provided with an unusually supportive network of professionals. This availability may have promoted a sense of well-being secondary to the high level of support provided by the health professionals. The observation that the patients from the lowest rather than the highest socioeconomic stratum had a lower event rate of psychiatric symptoms when they were followed in the intensive treatment program could reflect the benefit of such supportive interventions by members of the treatment team in patients at higher risk for psychiatric problems.
3. Patients in the intensive treatment group achieved a mean level of glycemic control above the nondiabetic glycemic range or study target (8). Only 5% of the subjects maintained an HbA_{1c} level within the normal range throughout the study (8). Therefore, it is likely that patients who found the demands of intensive therapy too burdensome chose to reduce their efforts from time to time. Patients whose treatment became too demanding could decrease their attention to their diabetes to meet the needs of their day-to-day life.

   Patients may use quality-of-life considerations as a basis for treatment decisions. When the demands of treatment, or its consequences, begin to influence quality of life adversely, patients may modify treatment goals. Indeed, one rationale for including quality-of-life assessments in clinical trials such as the DCCT is to provide patients information to help them choose treatment strategies consistent with their lifestyles. In essence, patients may recognize the impact of a treatment on the quality of their lives and make continuous modifications in treatment objectives to match desirable quality-of-life objectives.
4. The measures used in this study may not have been sufficiently sensitive to group differences to detect clinically meaningful changes in quality of life. The fact that three different measures failed to detect any effects is somewhat reassuring. An ancillary study (32) of a subset of DCCT patients ($n = 939$) found positive effects of intensive treatment on patients' views about their diabetes. The differences between the groups were small but certainly did not indicate any negative consequences of intensive treatment on patient perceptions of diabetes-related stress (32).
5. Patients were carefully screened and selected. During the extensive screening process, patients who reported problems with any aspect of the protocol could be excluded. A history of psychiatric problems was used as a basis for exclusion. The informed consent and screening procedures were designed to identify highly motivated research subjects (9,10). On average, these patients were highly educated and came from higher social-class strata than the general population. Thus, the DCCT volunteers might have been unusually able to deal with challenges of intensive diabetes management compared with other individuals.

At the end of the study, before the release of the results, all subjects were queried about their experience in the study. Results of this inquiry supplemented our formal evaluation of the quality-of-life impacts of the trial. Overall, 90% of the in-

tensively treated patients and 88% of the conventionally treated patients viewed their experiences in the trial as positive. Of patients in both groups, >95% would agree to participate again. A few aspects of the trial caused some concern, e.g., masking of some results for conventionally treated patients and performing 3:00 A.M. blood glucose tests for intensively treated patients. Nonetheless, it is particularly noteworthy that most of the intensively treated patients regarded the tasks of therapy (e.g., telephone calls, injections, clinic visits, and daytime blood tests) as positive rather than negative aspects of treatment. This positive perception of certain aspects of the trial in the intensive treatment group may have counterbalanced any negative effect of the increased frequency of hypoglycemia.

The only association between frequency of hypoglycemia during the study and quality of life was noted in the intensive treatment group using the SCL-90R. The study may not have had adequate power to detect an association between hypoglycemia and quality of life as measured by the DQOL. It is also possible that more severe hypoglycemic events, accumulated over a longer follow-up period or under circumstances that involved less careful follow-up, could lead to a greater impact of hypoglycemia on quality of life.

In summary, the findings of the DCCT provide compelling evidence that intensive diabetes management delays the onset and slows the progression of long-term complications of IDDM without a concomitant decrease in the quality of patients' lives. However, in translating the DCCT findings into clinical practice, it is important to realize that special circumstances may have led to the study's quality-of-life results. The use of intensive treatment techniques by patients who are already emotionally upset, are not fully supported by their families or health care providers, deny their illness, do not have adequate access to health care professionals, or are uncomfortable with the added demands of treatment may cause more problems with quality-of-life outcomes than were demonstrated in the DCCT (33). Intensification of therapy should only be undertaken when the patient understands and feels ready to try it and when there is adequate staff to provide support for the psychosocial as well as medical aspects of the treatment regimen.

Acknowledgments— This study was supported under cooperative agreements and a research contract with the Division of Diabetes, Endocrinology and Metabolic Diseases of the National Institute of Diabetes and Digestive and Kidney Diseases and by the National Heart, Lung and Blood Institute, the National Eye Institute, the National Center for Research Resources, and various corporate sponsors (listed in *Diabetes Care* 10:1–19, 1987).

References

1. Croog SH, Levine S, Testa MA, Brown B, Bulpitt CJ, Jenkins CD, Klerman GL, Williams GH: The effects of antihypertensive therapy on the quality of life. *N Engl J Med* 314:1657–1664, 1986
2. Testa MA, Sudilovsky A, Rippey RM, Williams GH: A short form for clinical assessment of quality-of-life among hypertensive patients. *Am J Prev Med* 5:82–89, 1989
3. Moinpour-McMillen C, Feigl P, Metch B, Hayden KA, Meyskens FL, Crowley J: Quality-of-life end points in cancer clinical trials: review and recommendations. *J Natl Cancer Inst* 81:485–495, 1989
4. Hurny C, Bernhard J: Problems in assessing quality-of-life (QL) in lung cancer patients in clinical trials. *Chest* 96 (Suppl. 1):102–105, 1989
5. Schoenberger JA, Croog SH, Sudilovsky A, Levine S, Baume RM for the Quality-of-life Research Group: Self-reported side effects from antihypertensive drugs: a clinical trial. *Am J Hypertens* 3:123–132, 1990
6. DCCT Research Group: DCCT design and methodological considerations for the feasibility phase. *Diabetes* 35:530–545, 1986
7. The Diabetes Control and Complications Trial (DCCT): Results of the feasibility study. *Diabetes Care* 10:1–9, 1987
8. DCCT Research Group: The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. *N Engl J Med* 329:977–986, 1993
9. Kramer J, Jacobson AM, Ryan CM, Murphy WD, and the DCCT Research Group: Psychological aspects of the Diabetes Control and Complications Trial. In *The Technology of Diabetes Care: Converging Medical and Psychosocial Perspectives*. Bradley C, Home P, Christie M, Eds. Harwood, NY, Churchill, 1991, p. 122–139
10. DCCT Research Group: Implementation of a multi-component process to obtain informed consent in the Diabetes Control and Complications Trial. *Controlled Clin Trials* 10:83–96, 1989
11. DCCT Research Group: Reliability and validity of a diabetes quality-of-life measure for the Diabetes Control and Complications Trial (DCCT). *Diabetes Care* 11: 725–732, 1988
12. Jacobson AM, de Groot M, Samson JA: The evaluation of two measures of quality-of-life in patients with type I and type II diabetes. *Diabetes Care* 17:267–274, 1994
13. Jacobson AM, The DCCT Research Group: The diabetes quality-of-life measure. In *Handbook of Psychology and Diabetes*. Bradley C, Ed. Reading, U.K., Hardwood, 1994, p. 65–87
14. Ware JH, Sherbourne CD: The MOS 36-item short form survey (SF-36). I. Conceptual framework and item selection. *Med Care* 30:473–483, 1992
15. National Center for Health Statistics: Current estimates from the National Health Interview Survey: United States (1989). In *Vital and Health Statistics*. Washington, DC, U.S. Govt. Printing Office, Series 10, no. 176, 1990
16. Nathan DM, Fogel N, Norman D, Russell PS, Tolkoff-Rubin N, Delmonico FL, Auchincloss H, Camuso J, Cosini AB: Long-term metabolic and quality-of-life results with pancreatic/renal transplantation in insulin-dependent diabetes mellitus. *Transplantation* 55:85–91, 1991
17. Derogatis LP, Rickels K, Rock A: The SCL-90 and MMPI: a step in validation of a new self-report scale. *Br J Psychiatry* 128: 280–289, 1976
18. Deragotis LR, Rickels K, Rock A: *The SCL-90R Administration Scoring and Procedural Manual I*. Baltimore, MD, Clinical Psychosomatic Research, 1977
19. EDIC Research Group: *Manual of Operations*. Rockville, MD, EDIC, 1994
20. Fryback DG, Dasbach ED, Klein R, Klein BEK, Martin PA, Dorn N, Petersen K: Health assessment by SF-36, quality of well-being index and time tradeoffs: predicting one measure from another. *Decision Making* 12:348, 1992
21. Stewart AL, Greenfield S, Hays RD: Functional status and well-being of patients with chronic conditions. *JAMA* 262:907–913, 1989
22. Wu AW, Rubin HR, Mathews WC, Ware JE, Brysk LT, Hardy WD, Bozzette SA, Spector SA, Richman DD: A health status questionnaire using 30 items from the Medical Outcomes Study. *Med Care* 29: 786–798, 1991
23. DCCT Research Group: Epidemiology of severe hypoglycemia in the DCCT. *Am J Med* 90:450–459, 1991
24. Snedecor GW, Cochran WG: *Statistical Methods*. 6th ed. Ames, Iowa State University Press, 1967
25. Lee ET: *Statistical Methods for Survival Data Analyses*. Belmont, CA, Lifetime Learning, 1980
26. Lachin JM, Wei LJ: Estimators and tests in

the analysis of multiple nonindependent 2×2 tables with partially missing observations. *Biometrics* 44:513–528, 1988
27. Lachin JM: Some large-sample distribution-free estimation and tests for multivariate partially incomplete data from the populations. *Stat Med* 11:1151–1170, 1992
28. McCullagh P, Nelder JA: *Generalized Linear Models*. 2nd ed. New York, Chapman & Hall, 1989
29. Rudolf M, Ahern J, Genel M, Bates S, Harding P, Hochstadt J, Quinlar D, Tamborlane W: Optimal insulin delivery in adolescents with diabetes: impact of intensive treatment on psychosocial adjustment. *Diabetes Care* 5 (Suppl. 1):53–57, 1982
30. Hirsch I, Farkas-Hirsch R, Skyler J: Intensive insulin therapy for type I diabetes mellitus. *Diabetes Care* 13:1265–1283, 1990
31. Seigler D, Lagreca A, Citrin W, Reeves M, Skyler J: Psychosocial effects of intensification of diabetic control. *Diabetes Care* 5 (Suppl. 1):19–23, 1982
32. Young-Hyman D, Peyrot M, Jacobson A, Schlundt D, Drotar D: Impact of intensive treatment on diabetes related attitudes and behaviors in the DCCT (Abstract). *Diabetes* 43 (Suppl. 1):7A, 1994
33. Brink S, Stewart C: Insulin pump treatment in insulin dependent diabetes mellitus: children, adolescents, and young-adults. *JAMA* 255:617–621, 1986