Adverse Events and Their Association With Treatment Regimens in the Diabetes Control and Complications Trial

THE DIABETES CONTROL AND COMPLICATIONS TRIAL RESEARCH GROUP

OBJECTIVE — To describe the incidence of adverse events associated with intensive versus conventional therapy of insulin-dependent diabetes mellitus (IDDM) as implemented in the Diabetes Control and Complications Trial (DCCT).

RESEARCH DESIGN AND METHODS — The DCCT was a randomized, controlled clinical trial conducted at 26 centers in the U.S. and 3 centers in Canada. All data were collected from patient notifications of events and/or standardized, quarterly interviews that were validated and analyzed at a data coordinating center as events per 100 patient-years. The 1,441 volunteers were between the ages of 13 and 39 with IDDM for 1–15 years. Average length of follow-up was 6.5 years (range 3–9). Subjects were randomly assigned to conventional or intensive diabetes treatment.

RESULTS — The two treatment groups did not differ in mortality, major morbidity secondary to accidents, or ketoacidosis. However, intensive therapy was associated with a threefold increase in the risk of severe hypoglycemia (for hypoglycemia requiring assistance, the event rate per 100 patient-years was 61.2 in the intensive treatment group versus 18.7 in the conventional treatment group; for hypoglycemia involving coma or seizure, the rate was 16.3 vs. 5.4). Intensive therapy was also associated with a 73% higher risk of becoming overweight. There was a 46% reduction in the incidence of vaginitis in the intensive treatment group, but there were no significant differences in the rates of other infections.

CONCLUSIONS — The major adverse effect of intensive therapy of IDDM is a threefold increase in the risk of severe hypoglycemia with potentially serious sequelae. An increased incidence of becoming overweight, the long-term significance of which has yet to be determined, was also observed. Because the results of the DCCT were attained in highly selected, healthy IDDM patients who received attentive clinical management and frequent health education, DCCT adverse event rates may not reflect incidence or prevalence rates that would be expected in nonselected populations or in other clinical settings.

From the Diabetes Control and Complications Trial (DCCT) Research Group. 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 5 January 1995 and accepted in revised form 21 July 1995.

BMI, body mass index; CSII, continuous subcutaneous insulin infusion; DCCT, Diabetes Control and Complications Trial; DKA, diabetic ketoacidosis; IDDM, insulin-dependent diabetes mellitus; MDI, multiple daily injection; M&M, Mortality and Morbidity Classification; WESDR, Wisconsin Epidemiologic Study of Diabetic Retinopathy.

Insulin-dependent diabetes mellitus (IDDM) is accompanied by long-term microvascular, neurological, and macrovascular complications. These complications, including retinopathy, nephropathy, neuropathy, and cardiac and peripheral vascular disease, account for most of the morbidity and mortality associated with IDDM (1). Since shortly after the introduction of insulin therapy, the role of metabolic control in the pathogenesis of these chronic complications has been a topic of vigorous debate (2).

Recently published results of the multicenter Diabetes Control and Complications Trial (DCCT) demonstrate conclusively that intensive therapy of IDDM that achieves near-normal glycemic control both delays the appearance and slows the progression of its microvascular and neurological complications (3). The intensive therapy regimen used three or more daily insulin injections or continuous subcutaneous insulin infusion (CSII) and frequent blood glucose testing to achieve blood glucose levels as close as possible to the normal range (4–6). Conventional therapy was designed to mimic routine diabetes management and consisted of no more than two insulin injections per day (7). Volunteers with IDDM randomly assigned to these two treatment groups were followed to ascertain outcomes related to the long-term complications of diabetes as well as adverse effects related to treatment or to other aspects of participation in the trial.

A principal objective of the DCCT was to protect volunteer safety while allowing an assessment of adverse effects versus treatment-associated benefits. Both treatment protocols were intended to maintain clinical well-being and to minimize the occurrence of severe hypoglycemia (8,9). Although clinic staffs were routinely masked to the measurements of study outcomes, thresholds for safety were established and clinics were alerted by the coordinating center when a patient reached a threshold that required action, such as retinopathy of sufficient severity

to require more frequent follow-up or laser photocoagulation. In addition, periodic monitoring of accumulating study-wide data by an independent data, safety, and quality review group provided assurance that patient safety was not jeopardized, i.e., that the conventional treatment did not result in inadequate care and that the intensive treatment regimen did not lead to unacceptable risk through overzealous pursuit of normoglycemia.

This report summarizes treatment-related adverse events documented in both treatment groups during the DCCT and compares these observations with available natural history data. All cases of mortality and major morbidity are reviewed, and the occurrence of hypoglycemic events and of overweight is also described in relation to treatment group. Other clinical events, such as symptoms of diabetes and episodes of infection, are also reported.

RESEARCH DESIGN AND METHODS

Design

The DCCT was a multicenter, randomized, controlled clinical trial (4). Twenty-six clinics across the U.S. and three clinics in Canada enrolled participants with IDDM from 1983 to 1989 and followed them until 1993. Volunteers were randomly assigned to receive either intensive or conventional therapy. With few and usually temporary exceptions, all diabetes care was provided by clinics participating in the DCCT. Intensive therapy involved the use of a regimen designed to maintain near-normal glucose levels while minimizing severe hypoglycemia (4). Conventional treatment was designed to maintain subjects in good health and free from symptoms related to hyper- or hypoglycemia. Glycemic levels were assessed by HbA_{1c} and capillary blood glucose profiles performed quarterly.

Eligibility and exclusion criteria

The clinical and biochemical selection criteria for patients participating in the DCCT have been described in detail (5,6,9). Major eligibility criteria included IDDM defined by ascertainment of C-peptide deficiency, age 13–39 years, and freedom from serious complications of diabetes. The primary prevention cohort was required to have IDDM duration of 1–5 years and no retinopathy at baseline. The secondary intervention cohort was required to have IDDM duration of 1–15 years and minimal-to-moderate background retinopathy at baseline.

Eligibility criteria excluded the following: patients at high risk for several adverse events (e.g., a history of frequent ketoacidosis, hypoglycemic coma, or seizure); patients with a known risk factor for vascular complications (e.g., hypercholesterolemia or hypertension); patients who were considered unlikely to comply with the demands of either the intensive or conventional treatment protocol; and patients who could not demonstrate an adequate understanding of the trial's purposes (4,9). Patients with drug addiction, chronic alcoholism, and major mental illness were also excluded.

During the 1-year feasibility period (phase 2, the first 278 patients recruited), volunteers with two or more hypoglycemic seizures or coma during the previous 5 years were eligible if these episodes were thought to be related to inappropriate medical management. After the feasibility phase, potential volunteers during the main recruitment were excluded if they had had, in the previous 2 years, more than two episodes of seizure or coma regardless of attributed causes or more than one episode of severe neurological impairment without warning symptoms of hypoglycemia.

Patients

Nearly 7,000 individuals made initial contact with the DCCT, which had recruitment goals of 700 subjects in each of the primary prevention and secondary intervention cohorts. At their first visit, 2,800 subjects either were ineligible immediately because of age, type of diabetes, IDDM duration, or presence of advanced complications or chose not to undergo further eligibility testing after being more fully informed about the study. An additional 2,500 individuals entered the 6- to 8-week period of eligibility testing but failed to pass one or more major inclusion criteria (e.g., C-peptide level) or elected not to participate before completing the entire test sequence; 425 subjects passed all formal eligibility tests but were not randomly assigned, generally because of a final decision by the volunteer against participation or a decision by the clinic staff that the patient was unlikely to adhere to the study protocol. Of 371 such subjects during the main recruitment (phase 3), 7 were excluded because a history of hypoglycemia unawareness or of repeated hypoglycemic coma was eventually obtained. Additional subjects who had these characteristics may have already been excluded because of other characteristics or earlier eligibility test results. A total of 1,441 subjects, 726 in the primary prevention cohort and 715 in the secondary intervention cohort, were randomly assigned to conventional or intensive therapy. A brief description of subject characteristics at baseline is given in Table 1. Subjects were followed for an average of 6.5 years (range 3–9).

Definitions of adverse events

The adverse events reported here include mortality, a major accident, hospitalization, hypoglycemia, ketoacidosis, overweight, hypertension, insulin pump catheter infections, and other clinical events such as symptoms of diabetes and other infections. The major focus of this report is adverse events associated with therapy rather than the long-term complications of disease. To ensure reliable ascertainment of these adverse events, strict definitions were provided in the *DCCT Manual of Operations* (9). Patients were asked to notify the clinic immediately if they had major adverse events (a major accident, hospitalization, severe hypoglycemia, or diabetic ketoacidosis managed at another health care facility). For major

Table 1—*Baseline characteristics*

	Conventional	Intensive
Number of patients	730	711
Women (%)	46	48
Patient-years of follow-up	4,775	4,733
Age (years)	26.5 ± 7.1	27.1 ± 7.1
Adolescent (%)	14.1	12.9
Race (% Caucasian)	96.4	96.6
HbA_{1c} (%)	9.1 ± 1.6	9.1 ± 1.6
Blood glucose profile (mean of 7 samples, mg/dl)	230.4 ± 79.3	234.0 ± 83.4
Duration of IDDM (years)		
Primary cohort	2.6 ± 1.4	2.6 ± 1.4
Secondary cohort	8.6 ± 3.7	8.9 ± 3.8
Prior hypoglycemic coma or seizure (%)		
Feasibility cohort (n = 278)	5.3	8.9
Full-scale trial cohort (n = 1,441)	5.4	3.9
Prior DKA requiring hospitalization (%)	4.5	5.8
Overweight (% of patients)		
Men (BMI > 27.8 kg/m^2)	8.6	5.5
Women (BMI > 27.3)	7.5	8.7
Systolic blood pressure (mmHg)	114.7 ± 11.7	113.4 ± 11.5
Diastolic blood pressure (mmHg)	72.8 ± 8.9	72.3 ± 8.8
Current smokers (%)	18.4	18.6

Data are means ± SD.

events, the clinic obtained all relevant information possible from hospital records, other physicians, police reports, etc. Data on other events (such as overweight, hypertension, or infections) were collected at scheduled quarterly visits. The outcomes reported in this manuscript are defined and ascertained as follows.

Mortality. Mortality is defined as death attributable to any cause. Motor vehicle fatalities included operator and nonoperator deaths due to accidents in motor vehicles.

Major accidents. Major accidents included all events that resulted in hospitalization or death. These fatal and nonfatal events were classified further by the type of accident, whether a motor vehicle was involved, and whether hypoglycemia played a role.

Severe hypoglycemia. Severe hypoglycemia was defined as an episode of hypoglycemia in which the patient required assistance with treatment from another person to recover; in addition, the blood glucose level had to be documented as <50 mg/dl and/or the clinical manifestations had to be reversed by oral carbohydrate, subcutaneous glucagon, or intravenous glucose. Patients were asked to report severe hypoglycemia immediately and were asked about the occurrence of any hypoglycemia at each quarterly visit.

Ketoacidosis. The diagnosis of ketoacidosis required that the following criteria be satisfied: *1*) blood glucose level >250 mg/dl; 2) the presence of large/moderate ketones in urine or serum; 3) at least one of the following: arterial blood pH <7.30, venous blood pH <7.25, or serum bicarbonate <15 mEq/l; and 4) treatment within a health care facility.

Overweight. Weight and height measurements obtained as part of quarterly clinical examinations were used to calculate body mass index (BMI) (kg/m^2). Men were considered overweight when BMI was ≥27.8 kg/m^2, and women were considered overweight when BMI was ≥27.3 kg/m^2 (10).

Hypertension. Hypertension was defined as either a sitting systolic pressure >140 mmHg or a diastolic pressure >90 mmHg on two consecutive measurements 1 month apart.

Catheter infection. An infection at the site of an insulin infusion catheter was defined as one that required antibiotic treatment and/or surgical incision for drainage.

Other clinical events. Data on other clinical events were obtained at each quarterly visit. Patients were questioned as to the frequency of nocturia and the number of 8-ounce glasses of liquid drunk daily. Infections reviewed included urinary tract infection (documented by a midstream clean-catch urine culture), postoperative or deep wound infections, respiratory tract infections (lower or upper), gastroenteritis with fever, and vaginitis requiring treatment. Quarterly visits also included foot examination for infection or ulcer. Although intensive-treatment patients were seen more often than conventional-treatment patients for purposes of blood glucose management, only the above symptoms and clinical events ascertained by a standard questionnaire on the quarterly visits were recorded as data. Psychologically adverse events were recorded quarterly, and psychological status was formally evaluated periodically. These data are reported elsewhere (11).

Classification and monitoring of adverse events

An independent Mortality and Morbidity Classification (M&M) Committee (made up of expert members who did not otherwise participate in the DCCT) reviewed and classified deaths and major accidents according to a set of prespecified procedures to determine whether the event was related to diabetes and, for accidents, whether hypoglycemia played a role. With 95% certainty as a criterion, each event was classified as to whether hypoglycemia played a role at all and, if so, whether hypoglycemia was a possible, probable, or principal cause of the event.

Table 2—*Adverse events by treatment group during trial*

	Conventional			Intensive				
	% with event	Number of events	Rate	% with event	Number of events	Rate	Relative risk	95% confidence interval
Death	0.55	4	0.084	0.98	7	0.148	1.74	(0.51-5.95)
Major accidents	3.0	24	0.5	3.8	27	0.6	1.21	(0.55-2.68)
DKA	8.1	88	1.8	10.0	93	2.0	1.07	(0.72-1.59)
Overweight, ever	26.9	180	5.0	41.5	275	8.7	1.73	(1.43-2.09)*
Hypertension, ever	11.5	84	1.9	10.8	77	1.8	0.93	(0.68-1.28)
Catheter infection while on pump	—	—	—	23.3	162	10.9	—	—
Hospitalization (all causes)	26.2	347	7.3	24.2	294	6.21	0.86	(0.66-1.13)
Hospitalization (hypoglycemia)	3.7	36	0.8	5.6	54	1.1	1.62	(0.96-2.76)

Conventional group: $n = 730$; intensive group: $n = 711$. Rate indicates rate per 100 patient-years of follow-up. Rates are based on repeated events, except for death, overweight, and hypertension, in which case rates are based on life-table hazard estimates of first event. Relative risks (intensive/conventional) are adjusted for baseline retinopathy (primary versus secondary). "Overweight, ever" includes patients who were overweight at baseline (conventional group = 61, intensive group = 49). Hospitalization refers to inpatient admission. *Significant at $P < 0.001$.

Classification was performed without knowledge of treatment group assignment (9). At regular intervals, the DCCT Data Safety and Quality Review Group, another independent expert panel (12), reviewed the accumulating data for treatment group differences with respect to retinal, renal, neurological, and cardiovascular outcomes, as well as for mortality, major morbidity, and other adverse events.

Adverse effects of treatment (i.e., hypoglycemia, diabetic ketoacidosis [DKA], and insulin infusion catheter infection) were also monitored by the Clinic Monitoring Group comprised of DCCT investigators and staff. Frequent occurrences of these treatment-related adverse events in specific clinics or in individual subjects prompted a thorough review of the events and instigated treatment changes aimed at preventing them. Study-wide and clinic-specific incidence rates of severe hypoglycemia were monitored monthly and were presented to and discussed with the entire DCCT study group to enhance awareness and generate strategies to reduce hypoglycemia.

Management of adverse events

To minimize morbidity and mortality as well as potential confounders of treatment group differences in outcomes, detailed guidelines were provided for the management of patients with DKA and hypoglycemia. Although pregnancy itself is not an adverse event, specific guidelines for its management were stipulated. Additional guidelines were provided for the diabetes management of patients requiring surgery and for the general management of patients with infection, myocardial infarction, renal insufficiency, hypertension, and psychiatric disorders (9).

Statistical analysis

Wilcoxon's rank-sum test was used to compare the two groups for ordinal and numerical variables, and the contingency χ^2 test was used for categorical variables (13). The life-table method was used to estimate the cumulative incidence of an event based on the time to first event (14). The difference between cumulative incidence curves was tested using the Mantel (log-rank) test (15). For recurrent events, the crude event rates are presented as number per 100 patient-years based on the ratio of the observed number of events to the total patient-years of exposure. The relative risk (intensive/conventional) was computed as the ratio of the crude event rates. The variance of the crude event rate and of the log relative risk are based on a distribution-free estimator that included an adjustment for overdispersion (16). All results that are nominally significant at $P < 0.05$ are indicated. Analyses were conducted separately for the primary prevention and the secondary intervention cohorts. However, because the results for the two cohorts are similar, the results are presented for both cohorts combined unless otherwise specified. For selected events, observed numbers in the DCCT were compared with those expected in a similarly aged U.S. general population (17). The reference populations were chosen from specified sources and were based on data from the late 1980s to reflect the most representative years of exposure during the DCCT. Because the observed and expected numbers were quite small and sampling errors were relatively large, no attempt was made to provide estimation error intervals.

RESULTS

Mortality

The death rate in the conventional group was 0.084 deaths per 100 person-years, and the rate in the intensive group was 0.148 ($P = 0.38$) (Table 2). Relevant facts about the 11 patients who died during the

Table 3—*Deaths in the DCCT*

Treatment group	Age at death (years)	Sex	Years in study	Cause of death	Hypoglycemia possible cause	Role of diabetes	Motor vehicle accident
Conventional	18	M	4.5	Suicide	No	None	No
	25	M	4.5	Acquired immunodeficiency syndrome	No	Minor	No
	34	M	0.3	Auto accident—driver	Yes	Minor	Yes
	42	M	3.8	Coronary artery disease	No	Minor	No
Intensive	22	M	5.9	Auto accident—driver	No	None	Yes
	27	M	2.4	Cardiac arrhythmia	No	None	No
	35	M	2.6	Auto accident—passenger	No	None	Yes
	36	M	6.7	Lung cancer	No	None	No
	38	M	1.7	DKA	No	Principal	No
	39	M	4.7	Coronary artery disease	No	Minor	No
	39	M	6.2	Tractor accident—driver	Yes	Minor	No

Role of diabetes classified by the M&M Committee (see METHODS).

study are listed in Table 3. All deaths occurred in men. Seven clinics each had a single death, and two clinics had two deaths each. Hypoglycemia was determined by the M&M Committee to be a possible cause of one death in each treatment group. The only death directly due to diabetes was from DKA in an intensive group patient treated with multiple daily injections (MDIs) who lapsed into coma at home without seeking medical attention. Three deaths were related to cardiovascular conditions. In two of these deaths, diabetes was determined to have a minor contributing role. One patient died of acquired immunodeficiency syndrome; the M&M Committee believed that his diabetic condition might have further compromised his ability to fight infection. Three DCCT deaths were attributable to motor vehicle accidents. In two of these accidents, the patient who died was the operator; the third accident was a passenger death. One other accidental death occurred in an intensive group patient while driving a tractor on a private farm. There was 1 suicide out of 10 attempts.

Major accidents

The 51 major accidents, including the 4 accidental deaths, are categorized in Table 4 by type and treatment group. Of these events, 27 occurred in conventionally treated patients and 27 occurred in intensively treated patients. The respective accident rates were 0.5 and 0.6 events per 100 patient-years (NS). The number of events of each type was also similar in the conventional and intensive groups. The most frequent type of major accident was that involving a motor vehicle (operator or nonoperator), with 14 events in the conventional group and 18 events in the intensive group.

Table 4 further examines the role of hypoglycemia in these major accidents as classified by the M&M Committee. In the conventional group, 9 accidents were judged to be related to hypoglycemia compared with 13 accidents in the intensive group. Hypoglycemia was judged to be the principal cause of 10 accidents, 4 in the conventional group and 6 in the intensive group. These treatment group differences were not statistically signifi-

Table 4—*Major accidents and role of hypoglycemia*

	Conventional	Intensive
Total events	24 (9)*	27 (13)†
Number of subjects	22	27
Women	10	7
Men	12	20
Accident type		
Motor vehicle accidents: operator	13 (9)	15 (9)
Motor vehicle accidents: nonoperator	1 (0)	3 (0)
Bicycle accidents	2 (0)	1 (1)
Accidents involving power tools	3 (0)	0 (0)
Other accidents	5 (0)	8 (3)
Role of hypoglycemia		
No role	15	14
Possible cause	5	5
Probable cause	0	2
Principal cause	4	6

Numbers in parentheses are events related to hypoglycemia (as possible, probable, or principal cause). *Includes 1 accidental death, possibly related to hypoglycemia. †Includes 3 accidental deaths (1 possibly related to hypoglycemia) and a hypoglycemia-related accident that caused death in a non-DCCT person. Since the numbers were quite small and sampling errors relatively large, no statistical tests were performed.

Table 5—*Symptoms associated with severe hypoglycemia episodes and associated sequelae*

	Hypoglycemic symptom (one symptom per episode)							
	All symptoms	Coma or seizure	Difficulty in awakening	Irrationality	Uncontrollable behavior	Confusion	Transient amnesia	Other
Total of symptoms	2,896:892	770:257	973:252	489:150	146:63	492:164	26:5	0:1
Associated sequelae (One per episode)								
1. Neurological damage	4:2	2:1	1:0	0:1	1:0	0:0	0:0	0:0
2. Injury requiring hospital	6:3	4:2	0:0	0:0	0:0	1:1	1:0	0:0
3. Injury to another person	16:1	5:0	2:0	7:0	0:0	2:1	0:0	0:0
4. Property damage	50:10	17:3	2:0	11:2	3:3	16:1	1:0	0:1
5. Traffic violation	8:4	1:1	0:0	4:1	1:0	2:2	0:0	0:0
No associated events	2,812:872	741:250	968:252	467:146	141:60	471:159	24:5	0:0

Ratios indicate intensive-to-conventional ratio. The most severe symptom associated with each hypoglycemic episode has been selected. The order of severity of the symptoms is listed from left to right of the table. The most severe associated sequelae of each episode has been chosen. The sequelae are listed in order of severity from top to bottom (items 1–5).

cant. One of the motor vehicle accidents caused by hypoglycemia in an intensive group patient resulted in the death of a non-DCCT passenger. Hypoglycemia was considered to be a probable cause of two accidents in the intensive group and a possible cause of five accidents in each treatment group.

Accidental morbidity not involving motor vehicles accounted for 10 events in the conventional treatment group and 9 events in the intensive group. The events that fall under "Other Accidents" in Table 4 include injuries secondary to burns, falls, sports injuries, etc.

Hospitalizations

The rates of hospitalization, excluding emergency room treatment, for all causes were 7.3 events per 100 patient-years in the conventional treatment group and 6.2 in the intensive treatment group (NS). Hospitalizations for hypoglycemia were also not significantly different between the treatment groups (Table 2).

Severe hypoglycemia

Hypoglycemia was the most common adverse event observed. A total of 3,788 hypoglycemic events in which the patient required assistance occurred during the study; of these events, 1,027 (27%) involved coma or seizure. Severe hypoglycemia, whether defined as all events or as events that involved coma or seizure, was ~3 times more frequent in the intensive than in the conventional group (Table 5; intensive:conventional = 2,896:892 and 770:257, respectively, $P < 0.001$). Two of the eleven deaths among DCCT patients (one in each treatment group) occurred in accidents of unknown cause. The lack of witnesses and other circumstances made it impossible either to incriminate or to exclude hypoglycemia as a cause; these deaths are not included in Table 5. Small proportions of the definite hypoglycemic events had nonlethal but significant occurrences associated with them such as neurological insult (0.16%), injury requiring hospitalization (0.24%), injury to another person requiring hospitalization (0.45%), property damage (1.58%), and traffic violations (0.32%). The frequency of these hypoglycemia-associated significant events within the intensive treatment group was always greater than or equal to the frequency in the conventional treatment group; however, these differences did not reach statistical significance. There were no associated myocardial infarctions or strokes.

Almost half of the DCCT cohort, 714 patients, had one or more episodes of hypoglycemia requiring assistance (Fig. 1*A*). Of these, 71% had multiple events. Nearly equal numbers in each treatment group (~14%) had only a single episode of severe hypoglycemia. However, by the end of the study, 50% of intensively treated patients had experienced more than one episode requiring assistance versus 21% of conventionally treated patients. For 10 or more episodes, the respective percentages were 14.2% of the intensive group and 2.5% of the conventional group. A total of 408 patients had one or more episodes involving coma or seizure (Fig. 1*B*). Coma or seizure made up 27% of all severe hypoglycemic events (26.6% in intensively treated and 28.8% in conventionally treated patients [Table 5]). Of the intensively treated patients, 17% had one episode of coma or seizure, compared with 12% of the conventionally treated patients. Of the patients who specifically experienced episodes of coma or seizure, 50% had multiple events. Of intensive treatment patients, 21% had more than one episode compared with 7% of conventional treatment patients. For five or more such episodes, the percentages were 6.6% vs. 1.4%, respectively.

All neuroglycopenic symptoms associated with episodes of severe hypoglycemia were recorded in standard categories by the clinics after each event. One symptom (short of coma or seizure)

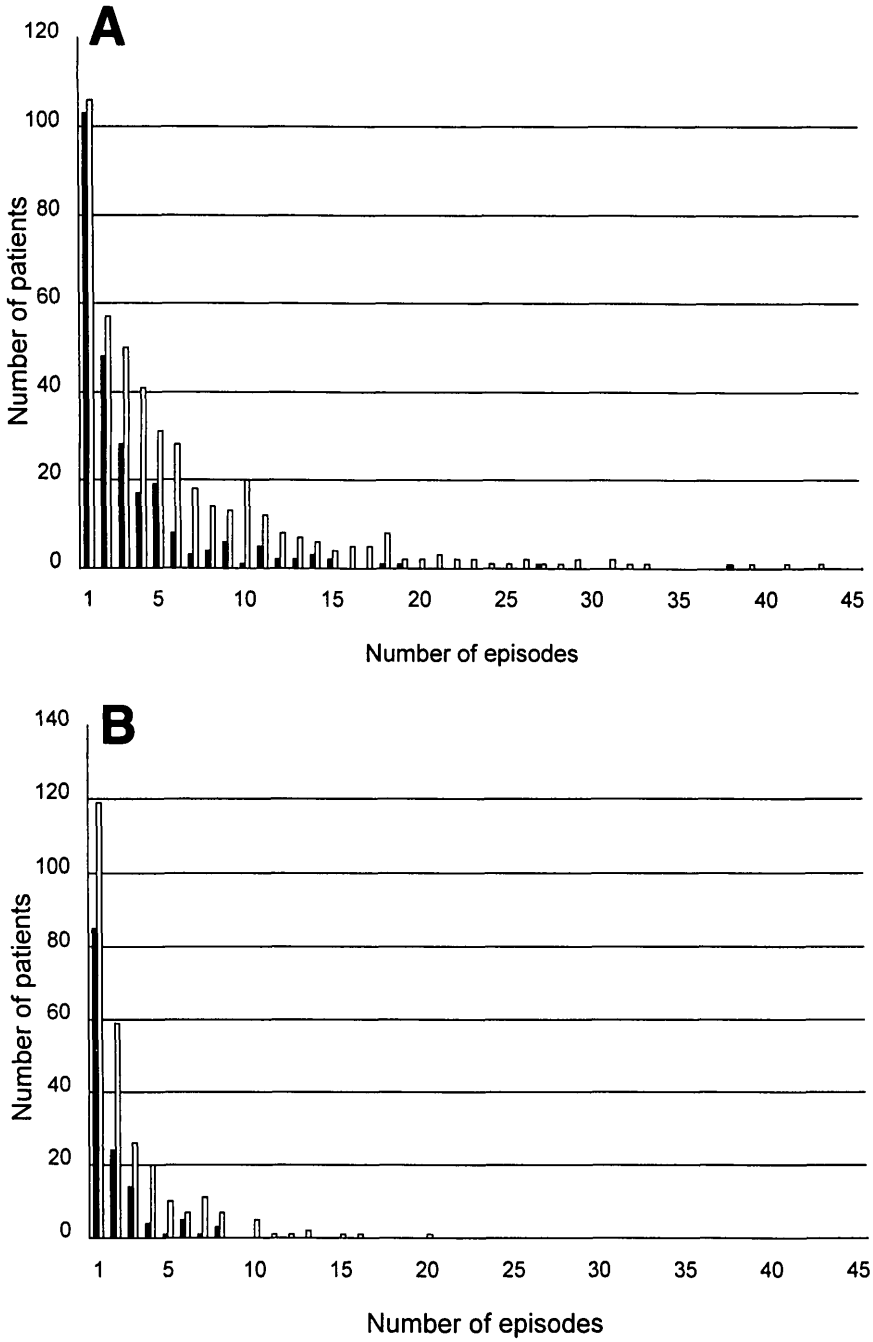

Figure 1—*Numbers of patients with one or more episodes of hypoglycemia in the conventional (■) and intensive (□) treatment groups. A: hypoglycemia events requiring assistance. Total number of episodes: conventional 892, intensive 2,896; total number of patients: conventional 255, intensive 459. B: hypoglycemia events with coma/seizure. Total number of episodes: conventional 257, intensive 770; total number of patients: conventional 137, intensive 271*

judged to be the most severe and dangerous is tabulated in Table 5 for each event. The high frequency of difficulty in awakening relates to the preponderance of severe hypoglycemia occurring during nighttime or during daytime periods of sleeping (18). The similar frequencies of confusion and irrationality may reflect some overlap in the way patients or family observers interpreted and reported these major symptoms.

As shown in Table 6, the event rate of hypoglycemia requiring assistance was 61.2 episodes per 100 patient-years of follow-up for the intensive group versus 18.7 for the conventional group (relative risk: 3.28, $P < 0.001$). For events involving coma or seizure, the event rate was 16.3 episodes per 100 patient-years of follow-up for the intensive group versus 5.4 for the conventional group (relative risk: 3.02, $P < 0.001$). The threefold increase in risk of hypoglycemia was observed throughout the study both for hypoglycemic episodes requiring assistance and for those episodes specifically causing coma or seizure. There was little, if any, downward trend in event rates with time in either category (Fig. 2).

The relative occurrence of severe hypoglycemia with intensive versus conventional treatment was analyzed in subgroups of subjects defined by baseline retinopathy status (primary prevention versus secondary intervention cohort) or by recruitment phase (feasibility versus full-scale trial) patients (Table 6). The relative risk of hypoglycemia with coma and seizure within the primary prevention cohort (intensive-to-conventional 4.26) was significantly greater than that within the secondary intervention cohort (intensive: conventional 2.47) ($P = 0.04$). This greater relative risk was due to a significantly lower event rate with conventional treatment in the primary prevention cohort versus conventional therapy in the secondary intervention cohort (3.4 vs. 7.3/100 patient-years, $P = 0.001$) (Table 6). We also examined the occurrence of hypoglycemic events separately for the feasibility phase patients versus the full-scale trial patients to evaluate the impact of the change in the eligibility criteria with regard to history of previous hypoglycemia on the frequency of hypoglycemia during the trial. Although patients in the feasibility study had higher rates of hypoglycemia than those in the full-scale study, the difference was not statistically

Table 6—*Hypoglycemic events in the DCCT by treatment group*

Hypoglycemic events	Conventional			Intensive			Relative risk	95% confidence interval
	% with event	Number of events	Rate	% with event	Number of events	Rate		
Requiring assistance	34.9	892	18.7	64.6	2,896	61.2	3.28	(2.65-4.05)*
Primary	27.8	349	15.2	59.5	1,173	55.0	3.61	(2.45-5.32)*
Secondary	42.6	543	21.9	69.4	1,723	66.3	3.02	(2.38-3.85)*
Feasibility phase patients	44.7	259	20.9	80.1	955	70.1	3.36	(2.30-4.89)*
Full-scale trial patients	32.8	633	17.9	60.5	1,941	57.6	3.22	(2.50-4.14)*
Coma or seizure	18.8	257	5.4	38.1	770	16.3	3.02	(2.36-3.86)*
Primary	13.0	77	3.4	35.1	305	14.3	4.26	(2.83-6.40)*
Secondary	25.0	180	7.3	41.1	465	17.9	2.47	(1.82-3.34)*
Feasibility	27.3	89	7.2	56.2	272	20.0	2.78	(1.79-4.33)*
Full-scale	16.9	168	4.8	33.5	498	14.8	3.11	(2.30-4.20)*

Conventional group: $n = 730$; intensive group: $n = 711$. Rate indicates rate per 100 patient-years of followup. Relative risk (intensive/conventional) for coma/seizure was significantly different between primary and secondary cohorts at $P = 0.04$. Rate of coma/seizure with conventional treatment in primary prevention cohort was significantly less than in the secondary intervention cohort $P = 0.001$. *Relative risk (intensive/conventional) was significant at $P < 0.001$.

significant ($P = 0.06$). Of note, the relative risk of hypoglycemia, comparing intensively treated patients with conventionally treated patients, was ~3.0 in the feasibility phase, as it was in the full-scale trial (Table 6).

DKA

DKA event rates were 2.0 per 100 patient-years in the intensive group (10.0% of patients) and 1.8 per 100 patient-years in the conventional group (8.1% of patients) (Table 2). Among intensively treated patients, rates were higher during periods of use of CSII pump (3.09/100 patient-years) than during use of MDI (1.39/100 patient-years, $P = 0.003$).

Overweight

The proportion of patients in the intensive treatment group who became overweight exceeded that in the conventional treatment group (Fig. 3). The pattern was uniform among men, women, adults, and adolescents. The incidence rate of becoming overweight was significantly higher in the intensively treated group, 8.7 vs. 5.0 cases per 100 patient-years at risk ($P = 0.001$) (Table 2). By the end of the study, 41.5% of the intensively treated patients had exceeded the overweight limits at some point during follow-up as compared with 26.9% of the conventionally treated patients ($P < 0.001$). The overall prevalence of overweight at the study close-out was 33.1% among the intensively treated patients versus 19.1% among the conventional patients.

Hypertension

Despite the disparity in the development of being overweight between treatment groups, the occurrence of hypertension was not significantly different between the treatment groups (1.8 cases/100 pa-

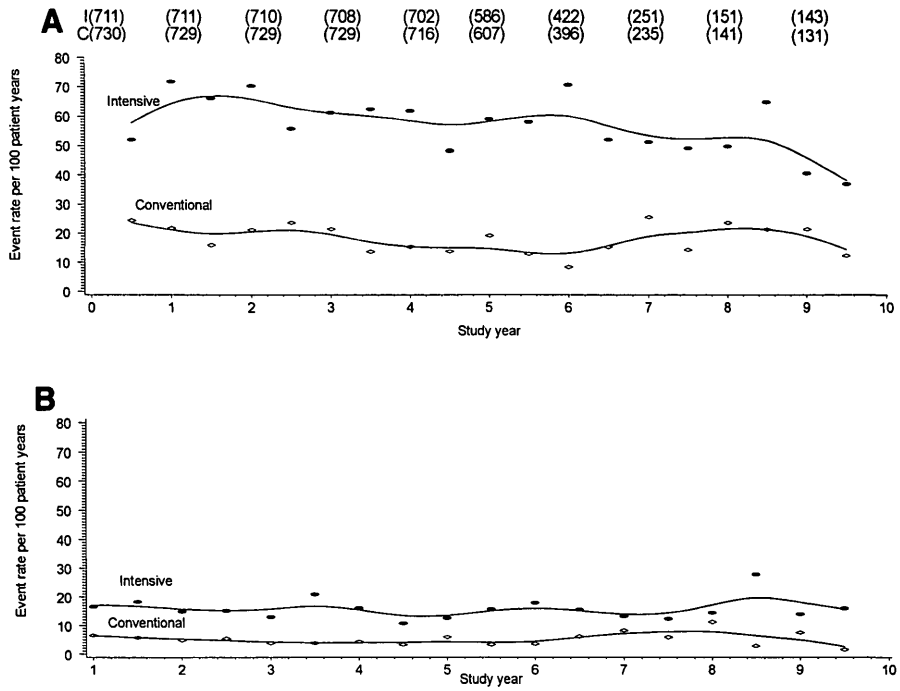

Figure 2—*Crude hypoglycemia event rates per 100 patient-years within 6-month intervals of study time with a smoothed spline function. Numbers on top are sample sizes at different time points. A: hypoglycemia events requiring assistance. B: hypoglycemia events with coma/seizure.*

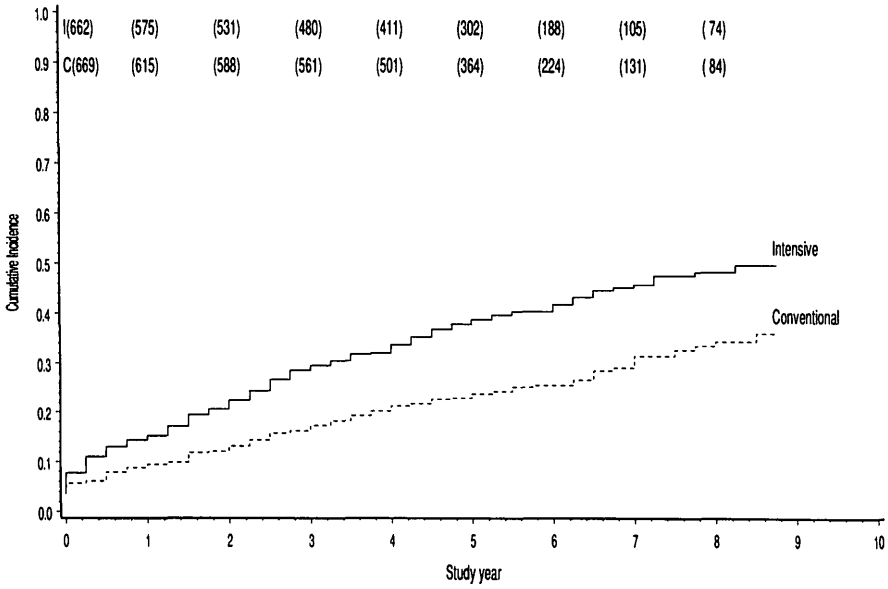

Figure 3—*Cumulative incidence of overweight. Patients who were overweight at baseline are excluded. Numbers on top are sample sizes. The difference between the treatment groups is statistically significant (log-rank statistic = 32.67, P < 0.001). The relative risk of intensive:conventional is 1.73, 95% confidence interval 1.43, 2.09.*

tient-years in the intensive group versus 1.9 in the conventional group, $P = 0.67$) (Table 2).

Insulin pump catheter infection

Insulin pump catheter infection occurred in intensive group patients using CSII at the rate of 10.9 infections per 100 patient-years of pump use.

Other clinical events

Compared with patients in the conventional group, patients in the intensive group experienced less frequent nocturia (35.0 ± 4.9 vs. 52.6 ± 6.2 nights with 1 episode per patient per year and 5.9 ± 2.1 vs. 10.3 ± 2.7 nights with 2 or more episodes per patient per year, $P < 0.0001$). Intensively treated patients also drank fewer 8-ounce glasses of liquid per day (8.5 ± 2.7 vs. 9.5 ± 3.0 glasses per person per day, $P < 0.0001$). The rates of occurrence of several common infections were compared between the two treatment groups. Vaginal infections requiring medical treatment were almost 50% lower in the intensive than the conventional group (17.9 vs. 33.2 events per 100 female patients per year, $P < 0.0001$). However, there was no significant difference in the frequency of either foot infections or foot ulcers (3.7 vs. 5.6 and 0.57 vs. 0.96 events per 100 patient-years, respectively, for intensive versus conventional groups) or in the occurrence of urinary, respiratory, or gastrointestinal tract infections.

CONCLUSIONS — The DCCT demonstrated the effectiveness of intensive treatment of IDDM in reducing the development and progression of diabetic complications when compared with conventional treatment (3). In this study, we have compared in detail the adverse event rates in the two randomly assigned treatment groups to assess more completely the balance between the benefits and risks of intensive treatment. Where possible, we have also compared the numbers of events observed in the DCCT patients with those expected in a similar sample from the U.S. general population (Table 7) or in other IDDM populations. As previously noted, the small numbers of certain major events made valid statistical comparisons unfeasible.

Eleven subjects died during the course of the DCCT, with no significant difference in mortality rates between the treatment groups. Using age- and sex-adjusted mortality rates for the general population of the U.S., 16 deaths would have been expected, with 12 in men and 4 in women (17) (Table 7). Therefore, the observed mortality rate in the DCCT was not excessive. Also, the death rate was not attributable to cardiovascular disease (20) (Table 7). In the general population, the age-adjusted mortality rate for women is 35% of the death rate for men, and therefore, fewer deaths in women would be expected in the DCCT because the female-to-male ratio in the study was very nearly 1. However, we have no explanation for the exclusive occurrence of deaths in men in the DCCT. Only one death was directly related to IDDM (DKA); in two other deaths, hypoglycemia could not be excluded as a contributing factor. There was one suicide among DCCT subjects along with nine attempted suicides. The suicide rate was in the expected range (20); the completion rate parallels some national estimates that 1 in 10 suicide attempts succeed (22).

It is difficult to find specific mortality data for a closely comparable IDDM population. The DCCT patients had a mean age of 27 years and a mean diabetes duration of 5.6 years at entry. Because the mean age of onset of IDDM in the U.S. is 15 years of age (23), a population-based age-matched random sample of comparison patients with IDDM would have had a longer mean duration of diabetes and, therefore, potentially would have had more diabetes-related deaths. The Wisconsin Epidemiologic Study of Diabetic Retinopathy (WESDR) (24) is a population-based sample of patients with IDDM. A subpopulation of 150 WESDR patients has been identified that is matched in age and duration of diabetes to the DCCT patients (25). In these 150 WESDR patients, 6 died during 10 years of follow-up. This

Table 7—*Observed versus expected numbers of events for selected adverse events*

	Observed	Expected
Deaths	11	15.9*
Men	11	11.8*
Women	0	4.1*
Motor vehicle deaths	3	2.6†
Cardiovascular deaths	3	2.0‡
Suicides	1	1.5§
Hospitalizations for accidents	51‖	78.1¶
Prevalence of overweight (%)		
Conventional	19.1	23.4
Intensive	33.1	23.9

"Expected" indicates events expected in the U.S. general population age-adjusted according to attained age of DCCT patients at the beginning of each follow-up year for the total length of study time. Prevalence of overweight is based on prevalence of overweight according to data of the Second National Health and Nutritional Examination Survey (1976–1980) (10). Rates were adjusted for sex and age and distribution of DCCT patients at close-out. *Based on data from the life-tables of total U.S. population, 1989, by National Center for Health Statistics (17). †Based on estimates from the National Traffic Safety Administration, 1988 (19). Includes operator and nonoperator fatalities on public roadways. ‡Based on cause-specific mortality data from the *Vital Statistics of the United States*, 1986, by the National Center for Health Statistics (20) for deaths due to major cardiovascular diseases (ICD codes 390–448). §Based on cause-specific mortality data from the *Vital Statistics of the United States*, 1986, by the National Center for Health Statistics (20) for deaths due to suicide (ICD codes E950–E959). ‖Major accidents requiring hospitalization. ¶Based on data from the National Hospital Discharge Survey (21); includes hospitalizations for injuries and burns (ICD codes 800–949) adjusted for sex and age. Observed and expected numbers were quite small and sampling errors relatively large; no attempt was made to provide estimation error intervals.

mortality rate of ~4 deaths per 1,000 patient-years is more than 3 times that observed in the DCCT. The death rate in another IDDM population that was age-comparable with the DCCT cohort was >10 times higher (26). However, these comparisons must be interpreted with caution, given that the DCCT patients were highly selected and had minimal or no diabetic complications at baseline, were otherwise healthy, and were willing to participate in a long-term randomized intervention study.

Patients in the conventional and intensive treatment groups demonstrated no difference in rates of hospitalization, excluding hospitalizations with the primary purpose of improving blood glucose control. Absolute rates of hospitalization for medical illnesses must be interpreted in light of the fact that most DCCT centers had access to a General Clinical Research Center where study patients could be hospitalized without cost. Nevertheless, hospitalizations for accidents did not exceed what would be expected of an age/sex-comparable general population (21) (Table 7).

By far, the most common serious adverse event was severe hypoglycemia. The rate of 19 events per 100 patient-years in the conventional group was within the wide range of older reports (27–31) but interestingly was much lower than that of two more recent prospective studies: 140 and 160 events per 100 patient-years (32,33). These latter rates exceed even that of the DCCT intensive treatment group (61 events per 100 patient-years). However, the validity of such comparisons is weakened by differences in definitions of severe hypoglycemia, methods of ascertainment, time intervals over which events were recorded or recalled, the populations studied, and methods of treatment. For similar reasons, the proportion of events manifest by coma or seizures and the prevalence of multiple events in DCCT subjects cannot be compared strictly with other reports.

The major conclusion with regard to adverse events is that intensive therapy increases the frequency of severe hypoglycemia two- to threefold. In particular, intensive treatment accentuated the risk of multiple episodes of hypoglycemia that required assistance with treatment and that caused coma or seizure (Fig. 1). However, the proportion of total episodes involving coma or seizure was not increased by intensive versus conventional therapy. Two smaller randomized clinical trials have also reported similar results (34,35), whereas others have claimed that intensive treatment is not associated with an increased risk of severe hypoglycemia (31). However, the careful ascertainment procedures of the DCCT in a large number of patients and the consistency of excess risk across numerous DCCT clinics (4) attests to the reality of this problem. Despite continuing emphasis on avoiding risk factors leading to hypoglycemia (18), the occurrence of severe hypoglycemic reactions did not diminish in either treatment group with duration of study participation (Fig. 2). In contrast with a previous report (36), in the DCCT, CSII did not decrease the risk of severe hypoglycemia when compared with MDI therapy; in fact, coma and convulsions occurred more frequently with CSII (4). We have also noted previously that the risk of severe hypoglycemia is inversely related to HbA_{1c} with intensive treatment (3).

There was a lesser tendency for coma or seizure to occur more than once in the subgroup of patients experiencing any such episodes than for severe hypoglycemia of any type requiring assistance to occur repeatedly (Fig. 1). The inherent risk of repetitive coma or seizure may simply be lower than that for less morbid hypoglycemic events. But it is also possible that one episode of coma or seizure particularly sensitizes family and other caregivers to the risks of hypoglycemia and leads to earlier intervention when hypoglycemia symptoms or signs of low glucose values first appear.

Despite their increased frequency of severe hypoglycemia accompanied by central nervous system manifestations, intensive treatment group subjects showed no trend toward worsening neuropsychological or cognitive functioning over time (3,11). Neurocognitive test scores in the intensive treatment group were not significantly different from those of the conventional group at the end of the study (11). Similar findings have been previously reported by the Stockholm Diabetes Intervention Study (35). No signif-

icant impairment of cognitive function occurred in DCCT subjects with as many as eight severe hypoglycemic episodes (11). While these observations are reassuring, they do not preclude the possibility that either longer-term exposure to multiple episodes or more sensitive testing methods will reveal cumulative deleterious effects of hypoglycemia.

Because of the possible negative effect of hypoglycemia on driving skills (37), fatalities caused by vehicle accidents are of special concern. Using U.S. national traffic fatality data (19) and age-adjusting them to the DCCT population, a total of 2.6 traffic fatalities would have been expected during the study. This figure is close to the three deaths observed in DCCT-patient accidents (two drivers plus one passenger).

Despite three times as many severe hypoglycemic reactions in the intensive treatment group, the number of major motor vehicle accidents attributable to hypoglycemia was similar in the two treatment groups. One possible explanation for this is the particular emphasis clinic staff placed on avoidance of hypoglycemia during driving. Early in the study, all of the clinics developed individual educational programs aimed at preventing hypoglycemia while operating a vehicle. Patients were instructed to check their blood glucose and/or eat before driving, to stop driving immediately if any hypoglycemic symptoms occurred, to have a carbohydrate available in the car at all times, and to test blood glucose frequently during long car trips. Nevertheless, hypoglycemia was independently judged to be a principal contributing factor in 36% and a possible factor in 43% of all nonfatal vehicle accidents. This compares with a retrospective report by Scottish patients who attributed 25% of their road accidents (severity not specified) to hypoglycemia (33).

The overall rate of hypoglycemia in the primary prevention cohort, independent of treatment group, was less than that in the secondary intervention cohort, perhaps because residual insulin secretion allowed better glycemic control on lower insulin doses (38–40). In addition, other risk factors for severe hypoglycemia may have worsened with prolonged duration of IDDM, such as impaired counterregulation to hypoglycemia (41). However, the relative risk of severe hypoglycemia with intensive therapy was actually greater in the primary prevention cohort than in the secondary intervention cohort. This was due, at least in part, to a lower event rate in the conventionally treated subjects of the primary prevention cohort than in those of the secondary intervention cohort.

Given the greater frequency of severe hypoglycemia with intensive treatment and its inverse relationship to the HbA_{1c} level achieved (3; DCCT Research Group, unpublished observations), it would be clinically useful to identify a patient risk factor profile that would contraindicate or compel greater caution in the use of such treatment. At present, however, only a previous history of repeated severe hypoglycemia, the occurrence of multiple episodes during intensive therapy, or the presence of hypoglycemia unawareness are useful predictors of increased risk (3,18,33,41,42; DCCT Research Group, unpublished obervations). It also bears emphasis that attempts to lower HbA_{1c} with only two daily injections of insulin may produce as many episodes of hypoglycemic coma as MDI but at a higher HbA_{1c} level (36).

Intensive therapy was also associated with both men and women becoming overweight more frequently than with conventional therapy (3,43,44). This difference was especially pronounced in the first 3 years of treatment but was maintained thereafter throughout the study. Similar trends were seen in the Stockholm Study (35). In a national population similar to the age and sex distribution of DCCT patients, the overall prevalence of overweight would be ~23% (10). At the end of the study, the prevalence of overweight condition for the conventionally treated patients (19.1%), therefore, was close to what would be expected, whereas the prevalence for the intensively treated patients was higher (33.1%) (Table 7).

This excessive weight gain can be attributed to accumulation of both fat (44,45) and lean body mass (44). It occurred despite extensive and repeated dietary education that was aimed particularly at limiting the amount of food ingested and substituting glucose tablets for more attractive sources of carbohydrate in the treatment of mild hypoglycemia. The differences in weight gain (or even in frequency of hypoglycemia) between intensive and conventional treatment groups cannot be attributed to major differences in their total insulin doses (0.67 vs. 0.62 $U \cdot kg^{-1} \cdot day^{-1}$) (4). On the other hand, coverage of anticipated ingestion of extra amounts of mealtime carbohydrate with additional regular insulin in the premeal bolus could have been a factor.

Intensively treated patients had a significant reduction in vaginitis requiring treatment but not in urinary, respiratory, gastrointestinal, or foot infections. While the rate of DKA was not significantly different between the treatment groups, CSII was associated with a higher frequency than MDI therapy. Catheter infections in patients treated with CSII occurred at a lower rate than in previous reports (29).

In conclusion, DCCT patients generally experienced lower rates of many adverse events than would be expected in a similar IDDM population. However, this experience with a highly selected and otherwise healthy patient population given rigorously close clinical monitoring and repeated preventive education cannot necessarily be generalized to other IDDM populations or clinical settings. Although the DCCT has shown that intensive insulin therapy was unequivocally beneficial, it also entailed sustained increased risks of severe hypoglycemia and weight gain. Therefore, efforts must be focused on established and new interventions that will minimize these risks and maximize safety as patients and treatment teams work to prevent the long-

term microvascular and neurological complications of IDDM.

Acknowledgments— This work was supported by the Division of Diabetes, Endocrinology, and Metabolic Diseases of the National Institute of Diabetes and Digestive and Kidney Diseases, National Institutes of Health, through cooperative agreements and a research contract. Additional support was provided by the National Heart, Lung and Blood Institute, the National Eye Institute, and the National Center for Research Resources.

References

1. Deckert T, Poulsen JE, Larsen M: Prognosis of diabetics with diabetes onset before the age of thirty-one. *Diabetologia* 14: 363–377, 1978
2. Schade DS, Santiago JV, Skyler JS, Rizza RA: Effects of intensive treatment on long-term complications. In *Intensive Insulin Therapy*. Amsterdam, Excerpta Medica, 1983, p. 71–88
3. The Diabetes Control and Complications Trial 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
4. DCCT Research Group: Implementation of treatment protocols in the Diabetes Control and Complications Trial (DCCT). *Diabetes Care* 18:361–376, 1995
5. DCCT Research Group: Diabetes Control and Complications Trial (DCCT): results of feasibility study. *Diabetes Care* 10:1–19, 1987
6. DCCT Research Group: Diabetes Control and Complications Trial (DCCT): update. *Diabetes Care* 13:427–433, 1990
7. The DCCT Research Group: Treatment regimen design in the Diabetes Control and Complications Trial (DCCT). *Transplant Proc* 18:1678–1680, 1986
8. The DCCT Research Group: *DCCT Protocol*. Springfield, VA, U.S. Dept. of Commerce, National Technical Information Service (PB 88–116462-AS), 1988
9. The DCCT Research Group: *DCCT Manual of Operations*. Springfield, VA, U.S. Dept. of Commerce, National Technical Information Service (PB 93–182282), 1993
10. Williamson DF: Descriptive epidemiology of body weight and weight change in U.S. adults. *Ann Intern Med* 119:646–649, 1993
11. The DCCT Research Group: Effects of intensive diabetes therapy on neuropsychological functions in adults in the DCCT. *Ann Intern Med*. In press
12. Siebert C, Clark DM Jr: Operational and policy considerations of data monitoring in clinical trials: the Diabetes Control and Complications Trial experience. *Controlled Clin Trials* 14:30–44, 1993
13. Snedecor GW, Cochran WG: *Statistical Methods*. 6th ed. Ames, IA, Iowa State University Press, 1967
14. Lee ET: *Statistical Methods for Survival Data Analysis*. Belmont, CA, Lifetime Learning, 1980, p. 88–92, 127–129, 306–312
15. McCullagh P, Nelder JA: *Generalized Linear Models*. 2nd ed. New York, Chapman & Hall, 1989, p. 194–200, 429–430
16. Kleinbaum DG, Kupper LL, Morgenstern H: *Epidemiological Research: Principles and Quantitative Methods*. Belmont, CA, Lifetime Learning, 1982, p. 359
17. National Center for Health Statistics: *Vital Statistics of the United States, 1989*. Vol. II, Sec. 6. Washington, DC, U.S. Public Health Service, 1992
18. The DCCT Research Group: Epidemiology of severe hypoglycemia in the Diabetes Control and Complications Trial. *Am J Med* 90:450–459, 1991
19. National Highway Traffic Safety Administration (Fatal Accident Reporting System): Alcohol-related traffic fatalities. *MMWR* 41:895–897, 1992
20. National Center for Health Statistics: *Vital Statistics of the United States, 1986*. Vol. II, Part A. Washington, DC, U.S. Public Health Service, U.S. Govt. Printing Office, 1988, ([PHS] DHHS pub. no. 88–1122)
21. National Center for Health Statistics: National Hospital Discharge Survey. National Technical Information Service Data Tape no. PB92–500818.
22. Lester D: *Understanding and Preventing Suicide: New Perspectives*. Springfield, IL, CC Thomas,1990, p. 5–7
23. Bennet PH: Epidemiology of diabetes mellitus. In *Diabetes Mellitus: Theory and Practice*. Rifkin H, Porte D, Eds. New York, Elsevier, 1990, p. 357–377
24. Moss SE, Klein R, Klein BEK, Meuer SM: The association of glycemia and cause-specific mortality in a diabetic population. *Arch Intern Med* 154:2473–2479, 1994
25. The DCCT Research Group, Klein R, Moss S: A comparison of the study populations in the Diabetes Control and Complications Trial (DCCT) and the Wisconsin Epidemiologic Study of Diabetic Retinopathy (WESDR). *Arch Intern Med* 155:745–754, 1995
26. Dorman JS, Laporte RE, Kuller LH, Cruickshanks KJ, Orchard TJ, Wagener DK, Becker DJ, Cavender DE, Drash AL: The Pittsburgh Insulin-Dependent Diabetes Mellitus (IDDM) Morbidity and Mortality Study: mortality results. *Diabetes* 33:271–276, 1984
27. Goldstein DE, England JD, Hess R, Rawlings SS, Walker B: A prospective study of symptomatic hypoglycemia in young diabetic patients. *Diabetes Care* 4:601–605, 1981
28. Goldgewicht C, Slama G, Papoz L, Tchobroutsky G: Hypoglycemic reactions in 172 type (insulin-dependent) diabetic patients. *Diabetologia* 24:95–99, 1983
29. Mecklenburg RS, Benson EA, Benson JW, Fredlund PN, Guinn T, Metz RJ, Nielsen RL, Sannar CA: Acute complications associated with insulin infusion pump therapy: report of experience with 161 patients. *JAMA* 252:3265–3269, 1984
30. Casparie AF, Elving LD: Severe hypoglycemia in diabetic patients: frequency, causes, prevention. *Diabetes Care* 8:141–145, 1985
31. Mulhauser I, Berger M, Sonnenberg G, Koch J, Jorgens V, Schernthaner G, Scholz V, Padagogin D: Incidence and management of severe hypoglycemia in 434 adults with insulin-dependent diabetes mellitus. *Diabetes Care* 8:268–273, 1985
32. Pramming S, Thorsteinsson B, Bendston I, Binder C: Symptomatic hypoglycemia in 411 type 1 diabetic patients. *Diabetic Med* 8:217–222, 1990

33. MacLeod KM, Hepburn DA, Frier BM: Frequency and morbidity of severe hypoglycemia in insulin-treated diabetic patients. *Diabetic Med* 10:238–245, 1993
34. Dahl-Jorgensen K, Brinchmann-Hansen O, Hanssen KF, Ganes T, Kierulf P, Smeland E, Sandvik L, Aagenaes O: Effect of near normoglycemia for two years on progression of early diabetic retinopathy, nephropathy, and neuropathy: the Oslo study. *Br Med J* 293:1195–1200, 1986
35. Reichard P, Phil M: Mortality and treatment side-effects during long-term intensified conventional insulin treatment in the Stockholm Diabetes Intervention Study. *Diabetes* 43:313–317, 1994
36. Dahl-Jorgensen K: Near-normoglycemia and late diabetic complications: the Oslo study. *Acta Endocrinol* 115 (Suppl. 284): 1–38, 1981
37. Cox DJ, Gonder-Frederick L, Clarke W: Driving decrements in type I diabetes during moderate hypoglycemia. *Diabetes* 42:239–243, 1993
38. The DCCT Research Group: Effects of age, duration and treatment of insulin-dependent diabetes mellitus on residual β-cell function: observations during eligibility testing for the Diabetes Control and Complications Trial (DCCT). *J Clin Endocrinol Metab* 65:30–37, 1987
39. Fukuda M, Tanaka A, Tahara Y, Ikegami H, Yamamoto Y, Kumahara Y, Shima K: Correlation between minimal secretory capacity of pancreatic β-cells and stability of diabetic control. *Diabetes* 37:81–88, 1988
40. Nakanishi K, Kobayashi T, Miyashita H, Ohkubo M, Sugimoto T, Murase T, Kosaka K, Inouye K, Kono M: Relationships among islet cell antibodies, residual beta cell function, and metabolic control in patients with insulin dependent diabetes mellitus of long duration: use of a sensitive C-peptide radioimmunoassay. *Metabolism* 39:925–930, 1990
41. Cryer PE, Binder C, Bolli GB, Cherrington AD, Gale EAM, Gerich JE, Sherwin RS: Hypoglycemia in IDDM. *Diabetes* 38: 1193–1199, 1989
42. Gold AE, MacLeod KM, Brier B: Frequency of severe hypoglycemia in patients with type I diabetes with impaired awareness of hypoglycemia. *Diabetes Care* 17:697–703, 1994
43. The DCCT Research Group: Weight gain associated with intensive therapy in the Diabetes Control and Complications Trial. *Diabetes Care* 11:567–573, 1988
44. The DCCT Research Group: Influence of intensive diabetes treatment on weight and composition of adults in the Diabetes Control and Complications Trial (Abstract). *Diabetes* 44 (Suppl.1):29A, 1995
45. Carlson MG, Campbell PJ: Intensive insulin therapy and weight gain in IDDM. *Diabetes* 42:1700–1707, 1993